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(54) Title: SULFONAMIDE COMPOUNDS AS CYSTEINE PROTEASE INHIBITORS

(57) Abstract: The present invention is directed to compounds of formula ( I ) that are inhibitors of cysteine proteases, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is directed to pharmaceutical compositions comprising these compounds and processes for preparing them. Wherein R3 is-alkylene-SO2NR5R6.

# SULFONAMIDE CONTAINING COMPOUNDS AS CYSTEINE PROTEASE INHIBITORS

## Field of the Invention

The present invention is directed to compounds that are inhibitors of cysteine proteases, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is also directed to pharmaceutical compositions comprising these compounds and processes for preparing them.

## State of the Art

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increased expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. For example, increased cathepsin B levels and redistribution of the enzyme are found in tumors; thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

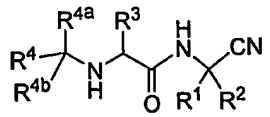
The prominent expression of cathepsin K in osteoclasts and osteoclast-related multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in osteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest that the enzyme plays a role in pulmonary disorders as well.

Cathepsin L is implicated in normal lysosomal proteolysis as well as in several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis, neuropathic pain, and Hashimoto's thyroiditis. In addition, cathepsin S is implicated in: allergic disorders, including, but not limited to asthma; and allogeneic immune reponses, including, but not limited to, rejection of organ transplants or tissue grafts.

In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules which inhibit the activity of this class of enzymes, in particular molecules which inhibit cathepsins B, K, L, F, and/or S, will therefore be useful as therapeutic agents.

## SUMMARY OF THE INVENTION

In a first aspect, this invention is directed to a compound of Formula (I):



(I)

wherein:

$R^1$ is hydrogen, alkyl, or haloalkyl;

$R^2$ is hydrogen, alkyl, or haloalkyl; or

$R^1$ and $R^2$ taken together with the carbon atom to which $R^1$ and $R^2$ are attached form cycloalkylene optionally substituted with one to four fluoro, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1,1-dioxohexahydrothiopyran-4-yl, piperidin-4-yl optionally substituted at the nitrogen atom of the piperidinyl ring with alkyl, haloalkyl, or cycloalkyl, or $-CH_2-O-CH_2-$;

$R^3$ is –alkylene-$SO_2NR^5R^6$ where:

$R^5$ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, –(alkylene)-$NR^7R^8$ [where $R^7$ is hydrogen, alkyl, acyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl and $R^8$ is haloalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocyloalkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonyl, aminosulfonyl, –C(O)$OR^9$ (where $R^9$ is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, or heterocycloalkyl) provided that $R^7$ is not hydrogen, alkyl, or –COR (where R is alkyl) when $R^8$ is aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl), or -$SO_2R^{10}$ (where $R^{10}$ is alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl)], acylalkyl, or heterocycloalkylaminocarbonyl; and

$R^6$ is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; or

$R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino or bridged azabicyclic ring;

wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ and the heterocycloamino and bridged azabicyclic rings formed by $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkylalkyl, heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or $-SO_2R^{11}$ (where $R^{11}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano, $-CONH_2$, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino;

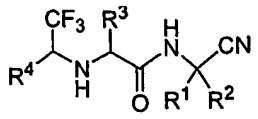
$R^4$ is hydrogen, alkyl, haloalkyl, aryl,heteroaryl, or heterocycloalkyl attached via a carbon ring atom, wherein the aromatic or alicyclic ring in $R^4$ is optionally substituted by one, two, or three $R^f$ independently selected from alkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, alkoxyalkyloxy, carboxy, alkoxycarbonyl, cyano, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino;

$R^{4a}$ is $-CHF_2$, $-CF_3$, $-CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CCl_2CF_3$, $-CF_2CHF_2$, $-CF_2CF_2CF_3$, or $-CF_2CF_2CHF_2$; and

$R^{4b}$ is hydrogen or haloalkyl; or

a pharmaceutically acceptable salt thereof.

In a second aspect, this invention is directed to a compound of Formula (Ia):



(Ia)

wherein:

$R^1$ is hydrogen or alkyl;

$R^2$ is hydrogen or alkyl; or

$R^1$ and $R^2$ taken together with the carbon atom to which $R^1$ and $R^2$ are attached form cycloalkylene optionally substituted with one to four fluoro, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1,1-dioxohexahydrothiopyran-4-yl, or $-CH_2-O-CH_2-$;

$R^3$ is:

(i) –alkylene-$SO_2NR^5R^6$ where $R^5$ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or heterocycloalkylalkyl and $R^6$ is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; or $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ and heterocycloamino formed by $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or are optionally substituted with one or two $R^b$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, acyl, or aminocarbonyl and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or

(ii) –alkylene-$SO_2$-alkylene-heteroaryl or –alkylene-$SO_2$-haloalkylene-heteroaryl wherein the heteroaryl ring is optionally substituted with one, two, or three substituents independently selected from one, two, or three $R^e$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, amino, alkylamino, dialkylamino, or acyl;

$R^4$ is aryl or heteroaryl wherein the aromatic ring in $R^4$ is optionally substituted by one, two, or three $R^f$ independently selected from alkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, carboxy, or alkoxycarbonyl; or

a pharmaceutically acceptable salt thereof.

In a third aspect, this invention is directed to a pharmaceutical composition comprising a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof in admixture with

one or more suitable excipients.

In a fourth aspect, this invention is directed to a method for treating a disease in an animal mediated by cysteine proteases, in particular cathepsin S, which method comprises administering to the animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

In a fifth aspect, this invention is directed to processes for preparing compounds of Formula (I) or (Ia).

In a sixth aspect, this invention is directed to a method of treating a patient undergoing a therapy wherein the therapy causes an immune response, preferably a deleterious immune response, in the patient comprising administering to the patient a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof. Preferably, the immune response is mediated by MHC class II molecules. The compound of this invention can be administered prior to, simultaneously, or after the therapy. Preferably, the therapy involves treatment with a biologic. Preferably, the therapy involves treatment with a small molecule.

Preferably, the biologic is a protein, preferably an antibody, more preferably a monoclonal antibody. More preferrably, the biologic is Remicade®, Refacto®, Referon-A®, Factor VIII, Factor VII, Betaseron®, Epogen®, Enbrel®, Interferon beta, Botox®, Fabrazyme®, Elspar®, Cerezyme®, Myobloc®, Aldurazyme®, Verluma®, Interferon alpha, Humira®, Aranesp®, Zevalin® or OKT3.

Preferably, the treatment involves use of heparin, low molecular weight heparin, procainamide or hydralazine.

In a seventh aspect, this invention is directed to a method of treating immune response in an animal that is caused by administration of a biologic to the animal which method comprises administering to the animal in need of such treatment a therapeutically effective amount of a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof.

In an eigth aspect, this invention is directed to a method of conducting a clinical trial for a biologic comprising administering to an individual participating in the clinical trial a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof with the biologic.

In a ninth aspect, this invention is directed to a method of prophylactically treating a patient undergoing treatment with a biologic with a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof to treat the immune response caused by the biologic in the patient.

In a tenth aspect, this invention is directed to a method of determing the loss in the

efficacy of a biologic in an animal due to the immune response caused by the biologic comprising administering the biologic to the animal in the presence and absence of a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof.

In an eleventh aspect, this invention is directed to a method of improving efficacy of a biologic in an animal comprising administering the biologic to the animal with a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof.

In a twelfth aspect, this invention is directed to the use of a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament. Preferably, the medicament is for use in the treatment of a disease mediated by Cathepsin S.

In a thirteenth aspect, this invention is directed to the use of a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for combination therapy with a biologic, wherein the compound of this invention treats the immune response caused by the biologic. Preferably, the compound(s) of the invention is administered prior to the administration of the biological agent. Preferably, the compound(s) of the invention is administered concomitantly with the biological agent. Preferably, the compound(s) of the invention is administered after the administration of the biological agent.

## DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

"Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures e.g., cycloalkyl and heterocycloalkyl rings as defined herein.

"Alkyl" represented by itself means a straight or branched, saturated aliphatic radical containing one to six carbon atoms, unless otherwise indicated e.g., alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, and the like.

"Alkylene", unless indicated otherwise, means a straight or branched, saturated aliphatic, divalent radical having the number of one to six carbon atoms, e.g., methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), trimethylene ($-CH_2CH_2CH_2-$), tetramethylene ($-CH_2CH_2CH_2CH_2-$) 2-methyltetramethylene ($-CH_2CH(CH_3)CH_2CH_2-$), pentamethylene ($-CH_2CH_2CH_2CH_2CH_2-$), and the like.

"Alkoxy" refers to a –OR radical where R is an alkyl group as defined above e.g., methoxy, ethoxy, and the like.

"Alkylsulfonyl" refers to a $-SO_2R$ radical where R is an alkyl group as defined above

e.g., methylsulfonyl, ethylsulfonyl, and the like.

"Alkylsulfonylamino" refers to a $-NHSO_2R$ radical where R is an alkyl group as defined above e.g., methylsulfonylamino, ethylsulfonylamino, and the like.

"Alkoxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one alkoxy group, preferably one or two alkoxy groups, as defined above, e.g., 2-methoxy-ethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like.

"Alkoxyalkyloxy" refers to a –O-(alkylene)OR radical where R is alkyl group as defined above, e.g., methoxyethyloxy and the like.

"Alkoxycarbonyl" refers to a –C(O)OR radical where R is an alkyl group as defined above e.g., methoxycarbonyl, ethoxycarbonyl, and the like.

"Alkoxycarbonylalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one, preferably one or two, alkoxycarbonyl group(s) as defined herein e.g., methoxycarboxymethyl, ethoxycarbonylmethyl, methoxycarbonylethyl, and the like.

"Aminoalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one, preferably one or two, -NRR' where R is hydrogen, alkyl, or $-COR^a$ where $R^a$ is alkyl, and R' is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cyloalkyl or cycloalkylalkyl as defined herein e.g., aminomethyl, methylaminoethyl, dimethylaminoethyl, 1,3-diaminopropyl, acetylaminopropyl, and the like.

"Acyl" refers to a –COR radical where R is hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkyl as defined herein, e.g., formyl, acetyl, trifluoroacetyl, benzoyl, piperazin-1-ylcarbonyl, and the like. When R is alkyl, the acyl group is referred to herein as alkylcarbonyl.

"Acylalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one, preferably one or two, acyl group(s) as defined herein e.g., methylcarbonylmethyl, benzoylethyl, piperidin-1-ylcarbonylmethyl or ethyl, and the like.

"Amino" means $-NH_2$ radical.

"Alkylamino" or "dialkylamino" refers to a –NHR and –NRR' radical respectively, where R and R' are independently alkyl group as defined above e.g., methylamino, dimethylamino, and the like.

"Aminocarbonyl" means –CONRR' radical where R and R' are independently selected

from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkylalkyl as defined herein. When the R group is H or alkyl and R' is alkyl, such groups may be referred to in this Application as alkylaminocarbonyl and dialkylaminocarbonyl respectively and are subset of aminocarbonyl group e.g., methylaminocarbonyl or dimethylaminocarbonyl.

"Aminosulfonyl" means $-SO_2NRR'$ radical where R and R' are independently selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkylalkyl or R and R' together with the nitrogen atom to which they are attached form heterocycloamino as defined herein.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

"Aromatic" refers to a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are $sp^2$ hybridized and the total number of pi electrons is equal to 4n+2.

"Aryl" refers to a monocyclic or fused bicyclic ring assembly containing 6 to 10 ring carbon atoms wherein each ring is aromatic e.g., phenyl or naphthyl.

"Aryloxy" refers to a –O-R radical where R is aryl as defined above e.g., phenoxy, napthyloxy, and the like.

"Aryloxycarbonyl" refers to a –C(O)O-R radical where R is aryl as defined above e.g., phenyloxycarbonyl, naphthyloxycarbonyl, and the like.

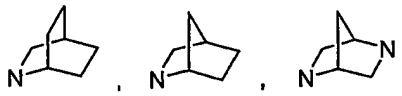
"Aralkyl" refers to a –(alkylene)-R radical where R is aryl as defined above e.g., benzyl, phenethyl, and the like.

"Aralkyloxy" refers to a –O-R radical where R is aralkyl as defined above e.g., benzyloxy, phenethyloxy, and the like.

"Aralkyloxycarbonyl" refers to a –C(O)O-R radical where R is aralkyl as defined above e.g., benzyloxycarbonyl, phenethyloxycarbonyl, and the like.

"Biologic" means a therapeutic agent originally derived from living organisms for the treatment or management of a disease. Examples include, but are not limited to, proteins (recombinant and plasma derived), monoclonal or polyclonal, humanized or murine antibodies, toxins, hormones, and the like. Biologics are currently available for the treatment of a variety of diseases such as cancer, rheumatoid arthritis, and hemophilia.

"Bridged azabicyclic ring" means a bridged bicylic ring containing 7 or 8 ring atoms wherein one or two ring atoms are nitrogen and the remaining ring atoms being carbon. The ring is attached to the sulfonyl group via the nitrogen atom. Representative examples include, but are not limited to, the following:

 and the like.

"Carboxy" refers to -C(O)OH radical.

"Carboxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one, preferably one or two, carboxy group(s) e.g., carboxymethyl, carboxyethyl, and the like.

"Cycloalkyl" refers to a monovalent saturated monocyclic ring containing three to eight ring carbon atoms e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

"Cycloalkylalkyl" refers to a –(alkylene)-R radical where R is cycloalkyl as defined above e.g., cyclopropylmethyl, cyclobutylethyl, cyclobutylmethyl, and the like.

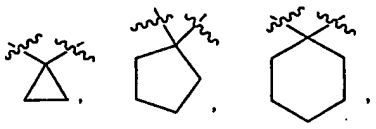
"Cycloalkylcarbonyl" refers to a –C(O)R radical where R is cycloalkyl as defined above e.g., cyclopropylcarbonyl, cyclohexylcarbonyl, and the like.

"Cycloalkylaminocarbonyl" refers to a –C(O)NHR radical where R is cycloalkyl as defined above e.g., cyclopropylaminocarbonyl, cyclohexylaminocarbonyl, and the like.

"Cycloalkyloxycarbonyl" refers to a –C(O)OR radical where R is cycloalkyl as defined above e.g., cyclopropyloxycarbonyl, cyclohexyloxycarbonyl, and the like.

"Cycloalkylalkyloxycarbonyl" refers to a –C(O)OR radical where R is cycloalkylalkyl as defined above e.g., cyclopropylmethyloxycarbonyl, cyclohexyloxycarbonyl, and the like.

"Cycloalkylene" refers to a divalent saturated monocyclic ring containing three to eight ring carbon atoms. For example, the instance wherein "$R^1$ and $R^2$ together with the carbon atom to which both $R^1$ and $R^2$ are attached form cycloalkylene" includes, but is not limited to, the following:

 and the like.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Derived" means a similar agent can be traced to.

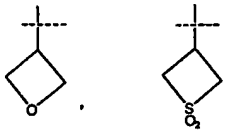
"Deleterious immune response" means an immune response that prevents effective

treatment of a patient or causes disease in a patient. As an example, dosing a patient with a murine antibody either as a therapy or a diagnostic agent causes the production of human antimouse antibodies that prevent or interfere with subsequent treatments. The incidence of antibody formation versus pure murine monoclonals can exceed 70%. (*see* Khazaeli, M. B. *et al. J. Immunother.* **1994**, *15*, pp 42-52; Dillman R. O. et al. *Cancer Biother.* **1994**, *9*, pp 17-28; and Reinsberg, J. *Hybridoma.* **1995**, *14*, pp 205-208). Additional examples of known agents that suffer from deleterious immune responses are blood-clotting factors such as factor VIII. When administered to hemophilia A patients, factor VIII restores the ability of the blood to clot. Although factor VIII is a human protein, it still elicits an immune response in hemophiliacs as endogenous factor VIII is not present in their blood and thus it appears as a foreign antigen to the immune system. Approximately 29-33% of new patients will produce antibodies that bind and neutralize the therapeutically administered factor VIII (*see* Lusher J. M. *Semin Thromb Hemost.* **2002**, 28(3), pp 273-276). These neutralizing antibodies require the administration of larger amounts of factor VIII in order to maintain normal blood clotting parameters; an expensive regimen of treatment in order to induce immune tolerance (*see* Briet E *et al. Adv. Exp. Med. Bio.* **2001**, *489*, pp 89-97). Another immunogenic example is adenoviral vectors. Retroviral therapy remains experimental and is of limited utility. One reason is that the application of a therapeutic virus generates an immune response capable of blocking any subsequent administration of the same or similar virus (*see* Yiping Yang *et al. J. of Virology.* **1995**, *69*, pp 2004-2015). This ensures that retroviral therapies must be based on the transient expression of a protein or the direct incorporation of viral sequence into the host genome. Directed research has identified multiple viral neutralizing epitopes recognized by host antibodies (*see* Hanne, Gahery-Segard *et al. J. of Virology* **1998**. *72*, pp 2388-2397) suggesting that viral modifications will not be sufficient to overcome this obstacle. This invention will enable a process whereby an adenoviral therapy will have utility for repeated application. Another example of an immunogenic agent that elicits neutralizing antibodies is the well-known cosmetic agent Botox. Botulin toxin protein, is purified from the fermentation of *Clostridium botulinum.* As a therapeutic agent, it is used for muscle disorders such as cervical dystonia in addition to cosmetic application. After repeated exposure patients generate neutralizing antibodies to the toxin that results in reduced efficacy (*see* Birklein F. *et al. Ann Neurol.* **2002**, *52*, pp 68-73 and Rollnik, J. D. *et al. Neurol. Clin. Neurophysiol.* **2001**, 2001(3), pp 2-4). A "deleterious immune response" also encompasses diseases caused by therapeutic agents. A specific example of this is the immune response to therapy with recombinant human erythropoietin (EPO). Erythropoietin is used to stimulate the growth of red cells and restore red

blood cell counts in patients who have undergone chemotherapy or dialysis. A small percentage of patients develop antibodies to EPO and subsequently are unresponsive to both therapeutically administered EPO and their own endogenous EPO (*see* Casadevall, N. *et al.*, *NEJM.* **2002**, *346*, pp 469-475). They contract a disorder, pure red cell aplasia, in which red blood cell production is severely diminished (*see* Gershon S. K. *et. al. NEJM.* **2002**, *346*, pp 1584-1586). This complication of EPO therapy is lethal if untreated. Another specific example is the murine antibody, OKT3 (a.k.a., Orthoclone) a monoclonal antibody directed towards CD-3 domain of activated T-cells. In clinical trials 20-40% of patients administered OKT3 produce antibodies versus the therapy. These antibodies, besides neutralizing the therapy, also stimulate a strong host immune reaction. The immune reaction is severe enough that patients with high titers of human anti-mouse antibodies are specifically restricted from taking the drug (*see* Orthoclone package label). A final example is a human antibody therapeutic. Humira® is a monoclonal antibody directed against TNF and is used to treat rheumatoid arthritis patients. When taken alone ~12% of patients develop neutralizing antibodies. In addition, a small percentage of patients given the drug also contract a systemic lupus erthematosus-like condition that is an IgG-mediated immune response induced by the therapeutic agent (*see* Humira package label).

Another example of "deleterious immune response" is a host reaction to small molecule drugs. It is known to those skilled in the art that certain chemical structures will conjugate with host proteins to stimulate immune recognition (see Ju. C. *et al.* **2002**. *Current Drug Metabolism 3*, pp 367-377 and Kimber I. *et al.* **2002**, *Toxicologic Pathology 30*, pp 54-58.) A substantial portion of these host reactions are IgG mediated. Specific "deleterious immune responses" that are IgG mediated include: hemolytic anemia, Steven-Johnson syndrome and drug induced Lupus.

"Four membered heterocycloalkyl" refers to a saturated monovalent monocyclic radical of 4 carbon ring atoms wherein one of the ring carbon atoms is replaced by a heteroatom selected from -NR- where R is hydrogen or a substituent as defined in the Summary of the Invention, -O-, -S-, -SO-, or $-S(O)_2-$. Representative examples include, but are not limited to, rings such as:



, and the like.

"Four membered heterocycloalkylcarbonyl" refers to a –COR radical where R is a four membered heterocycloalkyl as defined above.

"Four membered heterocycloalkyloxycarbonyl" refers to a –C(O)OR radical where R is a

four membered heterocycloalkyl as defined above.

"Four membered heterocycloalkyloxycarbonyl" refers to a –C(O)OR radical where R is a four membered heterocycloalkylalkyl as defined above.

"Halo" refers to fluoro, chloro, bromo or iodo.

"Haloalkyl" refers to alkyl as defined above substituted by one or more, preferably one to six, "halo" atoms, as such terms are defined in this Application. Haloalkyl includes monohaloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like e.g. chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Haloalkylene" means alkylene radical as defined above wherein one to four, preferably one or two hydrogen atoms in the alkylene chain has(have) been replaced by fluorine atom(s).

"Haloalkoxy" refers to a –OR radical where R is haloalkyl group as defined above e.g., trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, and the like.

"Heteroaryl" as a group or part of a group denotes an aromatic monocyclic or bicyclic moiety of 5 to 10 ring atoms in which one or more, preferably one, two, or three, of the ring atom(s) is(are) selected from nitrogen, oxygen or sulfur, the remaining ring atoms being carbon. Representative heteroaryl rings include, but are not limited to, pyrrolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyrazolyl, and the like.

"Heteroaryloxy" refers to a –O-R radical where R is heteroaryl as defined above e.g., furanyloxy, pyridinyloxy, indolyloxy, and the like.

"Heteroaryloxycarbonyl" refers to a –C(O)O-R radical where R is heteroaryl as defined above e.g., pyridinyloxycarbonyl, pyrimidinyloxycarbonyl, and the like.

"Heteroaralkyl" refers to a –(alkylene)-R radical where R is heteroaryl as defined above e.g., pyridinylmethyl, 1- or 2-furanylethyl, imidazolylmethyl, and the like.

"Heteroaralkyloxy" refers to a –O-R radical where R is heteroaralkyl as defined above e.g., pyridinylmethyloxy, furanylethyloxy, and the like.

"Heteroaralkyloxycarbonyl" refers to a –C(O)O-R radical where R is heteroaralkyl as defined above e.g., pyridinylmethyloxycarbonyl, pyrimidinylmethyloxycarbonyl, and the like.

"Heterocycloalkyl" refers to a saturated or partially unsaturated, monocyclic radical of 5 or 6 carbon ring atoms wherein one or more, preferably one, two, or three of the ring carbon atoms are replaced by a heteroatom selected from -N=, -N-, -O-, -S-, -SO-, or -$S(O)_2$- and further wherein one or two ring carbon atoms are optionally replaced by a keto (-CO-) group.

The heterocycloalkyl ring is optionally fused to cycloalkyl, aryl or heteroaryl ring as defined herein. Representative examples include, but are not limited to, imidazolidinyl, morpholinyl, thiomorpholinyl, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyranyl, 1,1-dioxotetrathiopyranyl, indolinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, 3,4-dihydroisoquinolinyl, dihydroindolyl, and the like.

When the heterocycloalkyl group contains at least one nitrogen ring atom it is referred to herein as "heterocycloamino" and is a subset of the heterocycloalkyl group as defined above.

"Heterocycloalkylalkyl" refers to a –(alkylene)-R radical where R is heterocycloalkyl as defined above e.g., pyrrolidinylmethyl, tetrahydrofuranylethyl, piperidinylmethyl, and the like.

"Heterocycloalkylaminocarbonyl" refers to a -CONHR radical where R is heterocycloalkyl as defined above e.g., tetrahydrofuranylaminocarbonyl, tetrahydropyranylaminocarbonyl, and the like.

"Heterocycloalkyloxycarbonyl" refers to a –O-R radical where R is heterocycloalkyl as defined above e.g., piperidinyloxy, tetrahydrofuranyloxy, and the like.

"Heterocycloalkylalkyloxycarbonyl" refers to a –C(O)O-R radical where R is heterocycloalkylalkyl as defined above e.g., piperidinylmethyloxycarbonyl, tetrahydrofuranylmethyloxycarbonyl, and the like.

"Hydroxy" means –OH radical. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like.

"Hydroxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

"Isomers" mean compounds of Formula (I) having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes

"optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center that has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has $2^{n-1}$ enantiomeric pairs, where $n$ is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula (I) are meant to encompasse all possible stereoisomers.

"Optional" or "optionally" or "may be" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "wherein the aromatic ring in $R^a$ is optionally substituted with one or two substituents independently selected from alkyl" means that the aromatic ring may or may not be substituted with alkyl in order to fall within the scope of the invention.

The present invention also includes *N*-oxide derivatives of a compound of Formula (I). *N*-oxide derivative mean a compound of Formula (I) in which a nitrogen atom is in an oxidized state (i.e., N→O) e.g., pyridine *N*-oxide, and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of Formula (I) or (Ia) which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid,

cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methylsulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxy-ethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

The present invention also includes prodrugs of a compound of Formula (I) or (Ia). Prodrug means a compound that is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of Formula (I) or (Ia). For example, an ester of a compound of Formula (I) or (Ia) containing a hydroxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Alternatively an ester of a compound of Formula (I) or (Ia) containing a carboxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of Formula (I) or (Ia) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methylsulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinates. Suitable esters of compounds of Formula (I) containing a carboxy group, are for example those described by Leinweber, F.J. *Drug Metab. Res.*, **1987**, *18*, page 379. An especially useful class of esters of compounds of Formula (I) containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard *et al.*, *J. Med. Chem.*, **1989**, *32*, pp 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of Formula (I) or (Ia) in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula (I) are useful in the preparation of compounds of Formula (I) or (Ia) in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" means any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

"Treatment" or "treating" with respect to combination therapy i.e., use with a biologic means any administration of a compound of the present invention and includes:

(1) preventing the immune response from occurring in an animal which may be predisposed to the immune response but does not yet experience or display the pathology or symptomatology of the immune response,

(2) inhibiting the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., reducing in degree or severity, or extent or duration, the overt manifestations of the immune response or reversing the pathology and/or symptomatology e.g., reduced binding and presentation of antigenic peptides by MHC class II molecules, reduced activation of T-cells and B-cells, reduced humoral and cell-mediated responses and, as appropriate to the particular immune response, reduced inflammation, congestion, pain, necrosis, reduced loss in the efficacy of a biologic agent, and the like).

The expression "wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ and the heterocycloamino formed by $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$

independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, acyl, aralkyloxycarbonyl, or aminocarbonyl" in the definition of $R^3$ in the compound of Formula (Ia) means that when $R^5$ and/or $R^6$ is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl; or when $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino, then the aromatic and/or alicyclic ring(s) in these groups is(are) either unsubstituted or substituted with $R^a$, or $R^b$ and $R^c$, or $R^c$ alone.

The expression "wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ and the heterocycloamino and bridged azabicyclic rings formed by $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, ...; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, acyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, heterocycloalkyloxycarbonyl, cycloalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, aminosulfonyl, or $-SO_2R^{11}$ (where $R^{11}$ is alkyl, aryl, heteroaryl, or heterocycloalkyl)..." in the definition of $R^3$ in the compound of Formula (I) means that when $R^5$ and/or $R^6$ is an aromatic or alicyclic ring(s) (e.g., $R^5$ and/or $R^6$ is cycloalkyl, aryl, etc.) or a group that contain an aromatic or alicylic ring (e.g., $R^5$ and/or $R^6$ is aralkyl, heterocycloalkylalkyl, etc.), these rings, whether directly or indirectly attached, are either unsubstituted or substituted with $R^a$, or $R^b$ and $R^c$, or $R^c$ alone.

## Preferred Embodiments

I. Certain compounds of Formula (I) within the broadest scope set forth in the Summary of the Invention are preferred. For example:

A. One preferred group of compounds is that wherein $R^1$ and $R^2$ are hydrogen.

B. Another preferred group of compounds is that wherein $R^1$ and $R^2$ together with the carbon atom to which they are attached form cycloalkylene, preferably $R^1$ and $R^2$ together with the carbon atom to which they are attached form cyclopropylene.

C. Another preferred group of compounds is that wherein $R^1$ and $R^2$ together with the

carbon atom to which they are attached form tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-dioxohexahydrothiopyran-4-yl.

1. Within the above preferred group (A-C), a more preferred group of compounds is that wherein $R^4$ is hydrogen and $R^{4b}$ is hydrogen.

2. Within the above preferred group (A-C), a more preferred group of compounds is that wherein $R^4$ is hydrogen and $R^{4b}$ is haloalkyl, preferably trifluoromethyl, 2,2,2-trifluoroethyl, or 2,2,3,3,3-pentafluoropropyl.

3. Within the above preferred group (A-C), another more preferred group of compounds is that wherein $R^4$ is alkyl, preferably methyl, ethyl, *n*- or *iso*-propyl, or *n*-, *iso*-, or *tert*-butyl and $R^{4b}$ is hydrogen.

4. Within the above preferred group (A-C), another more preferred group of compounds is that wherein $R^4$ is alkyl, preferably methyl, ethyl, *n*- or *iso*-propyl, or *n*-, *iso*-, or *tert*-butyl and $R^{4b}$ is haloalkyl, preferably trifluoromethyl, 2,2,2-trifluoroethyl, or 2,2,3,3,3-pentafluoropropyl.

5. Within the above preferred group (A-C), another more preferred group of compounds is that wherein $R^4$ is haloalkyl, preferably 2,2,2-trifluoroethyl or 2,2,3,3,3-pentafluoropropyl and $R^{4b}$ is haloalkyl, preferably 2,2,2-trifluoroethyl or 2,2,3,3,3-pentafluoropropyl.

6. Within the above preferred group (A-C), another more preferred group of compounds is that wherein $R^4$ is aryl optionally substituted with one, two or three $R^f$, preferably phenyl optionally substituted with one or two fluoro and $R^{4b}$ is hydrogen. Preferably, $R^4$ is phenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, or 3,4-difluorophenyl.

7. Within the above preferred group (A-C), another more preferred group of compounds is that wherein $R^4$ is aryl optionally substituted with one, two or three $R^f$, preferably phenyl optionally substituted with one or two fluoro and $R^{4b}$ is haloalkyl. Preferably, $R^4$ is phenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, or 3,4-difluorophenyl and $R^{4b}$ is trifluoromethyl.

8. Within the above preferred group (A-C), another more preferred group of compounds is that wherein $R^4$ is heteroaryl optionally substituted with one, two or three $R^f$, and $R^{4b}$ is hydrogen. Preferably, $R^4$ is indolyl, furanyl, thiophenyl, pyrrolyl, benzofuranyl, or benzothiophenyl optionally substituted with one, two $R^f$ independently selected from methyl, ethyl, methoxy, or fluoro.

(a) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where:

$R^5$ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, –(alkylene)-$NR^7R^8$ [where $R^7$ is hydrogen, alkyl, acyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl and $R^8$ is haloalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocyloalkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonyl, aminosulfonyl, –C(O)$OR^9$ (where $R^9$ is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, or heterocycloalkyl) provided that $R^7$ is not hydrogen, alkyl, or –COR (where R is alkyl) when $R^8$ is aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl), or -$SO_2R^{10}$ (where $R^{10}$ is alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl)], acylalkyl, or heterocycloalkylaminocarbonyl; and

$R^6$ is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; or

$R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino or bridged azabicyclic ring;

wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ and the heterocycloamino and bridged azabicyclic rings formed by $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkylalkyl, heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or –$SO_2R^{11}$ (where $R^{11}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano,

$-CONH_2$, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino;provided that:

(i) when $R^5$ is hydrogen, alkyl, acyl, or haloalkyl, then $R^6$ is not hydrogen or alkyl;

(ii) when $R^5$ is hydrogen, alkyl, or acyl and $R^6$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, then the aromatic or alicylic ring in these groups has to be substituted with an $R^c$ provided that: (a) $R^c$ is not alkoxycarbonyl or an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$; and

(iii) when $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino the heterocycloamino ring has to be substituted with an $R^c$ provided that: (a) $R^c$ is not alkoxycarbonyl or an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$.

Preferably, $R^5$ is methyl, ethyl, propyl, butyl, 2,2,2-trifluoroethyl, 2-hydroxethyl, 2- or 3-hydroxypropyl, 2-methoxy or ethoxyethyl, 2- or 3-methoxy or ethoxypropyl, methylaminoethyl, methylaminopropyl, acetylaminoethyl, 2-carboxyethyl, 3-carboxypropyl, methoxycarbonylethyl, acetyl, cyclopropyl, cyclopropylmethyl, benzyl, phenylethyl, pyridinylethyl, pyridinylmethyl, pyrimidinylmethyl, furanylmethyl, pyrrolylmethyl, indolylmethyl, quinolinylmethyl, isoquinolinylmethyl, or tetrahydroquinolinylmethyl and $R^6$ is hydrogen, methyl, ethyl, phenyl, benzyl, pyridinylmethyl or ethyl, pyrimidinylmethyl or ethyl, indolylmethyl or ethyl, quinolinylmethyl or ethyl, dihydroindolylmethyl or ethyl, piperidinylmethyl or ethyl, piperazinylmethyl or ethyl, pyrrolidinylmethyl or ethyl, or morpholinylmethyl or ethyl wherein the aromatic rings or alicyclic rings in $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from methyl, ethyl, trifluoromethyl, trifluoromethoxy, methoxy, hydroxy, or fluoro; or optionally substituted with one or two $R^b$ independently selected from hydrogen, methyl, ethyl, trifluoromethyl, methoxy, hydroxy, trifluoromethoxy, or fluoro and one $R^c$ selected from hydroxymethyl, hydroxyethyl, 2- or 3-hydroxypropyl, cyclopropylmethyl, phenyl, pyridinyl, benzyl, cyclopropyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, acetyl, trifluoroacetyl, benzyloxycarbonyl, dimethylaminocarbonyl, or methylaminocarbonyl; and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from methyl, ethyl, trifluoromethyl, methoxy, hydroxyl, trifluormethoxy or fluoro.

(b) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where:

$R^5$ is alkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, –(alkylene)$NR^7R^8$ [where $R^7$ is hydrogen, alkyl, acyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl and $R^8$ is hydroxyalkyl, alkoxyalkyl, carboxyalkyl alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonyl, aminosulfonyl, –C(O)$OR^9$ (where $R^9$ is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkyl) provided that $R^7$ is not hydrogen, alkyl, or –COR (where R is alkyl) when $R^8$ is aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl], acylalkyl, or heterocycloalkylaminocarbonyl and $R^6$ is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, acyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, heterocycloalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, aminosulfonyl, or $–SO_2R^{11}$ (where $R^{11}$ is alkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo.

Preferably, $R^5$ is 2-hydroxethyl, 2- or 3-hydroxypropyl, 2-methoxy or ethoxyethyl, 2- or 3-methoxy or ethoxypropyl, methylaminoethyl, methylaminopropyl, acetylaminoethyl, 2-carboxyethyl, 3-carboxypropyl, methoxycarbonylethyl, acetyl, cyclopropyl, cyclopropylmethyl, benzyl, phenylethyl, pyridinylethyl, pyridinylmethyl, pyrimidinylmethyl, furanylmethyl, pyrrolylmethyl, indolylmethyl, quinolinylmethyl, isoquinolinylmethyl, tetrahydroquinolinylmethyl or $–(CH_2)_2$-$NR^7R^8$ (where $R^7$ is methyl, ethyl, hydroxyethyl,

hydroxypropyl, or methoxyethyl and $R^8$ is hydroxyethyl, hydroxypropyl, methoxyethyl, methoxypropyl, phenyl, benzyl, cyclopropyl, or cyclopropylmethyl) and $R^6$ is hydrogen, methyl, ethyl, phenyl, benzyl, pyridinylmethyl or ethyl, pyrimidinylmethyl or ethyl, indolylmethyl or ethyl, quinolinylmethyl or ethyl, dihydroindolylmethyl or ethyl, piperidinylmethyl or ethyl, piperazinylmethyl or ethyl, pyrrolidinylmethyl or ethyl, or morpholinylmethyl or ethyl wherein the aromatic rings or alicyclic rings in $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from methyl, ethyl, trifluoromethyl, trifluoromethoxy, methoxy, hydroxy, or fluoro; or optionally substituted with one or two $R^b$ independently selected from hydrogen, methyl, ethyl, trifluoromethyl, methoxy, hydroxy, trifluoromethoxy, or fluoro and one $R^c$ selected from hydroxymethyl, hydroxyethyl, 2- or 3-hydroxypropyl, cyclopropylmethyl, phenyl, pyridinyl, benzyl, cyclopropyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, acetyl, trifluoroacetyl, benzyloxycarbonyl, dimethylaminocarbonyl, or methylaminocarbonyl; and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from methyl, ethyl, trifluoromethyl, methoxy, hydroxyl, trifluormethoxy or fluoro.

(c) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino substituted one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkylalkyl, heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or $–SO_2R^{11}$ (where $R^{11}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano,

-$CONH_2$, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino; provided that heterocycloamino ring is substituted with at least an $R^c$ provided that (a) $R^c$ is not an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$. Preferably, the heterocyclamino ring is piperazin-4-yl or piperidin—1-yl substituted at the 4-position with the groups described above.

Preferably, $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form 2,3-dihydroindol-1-yl, 1,3-dihydroisoindol-2-yl, 3,4-dihydroisoquinolin-2-yl, morpholinyl, piperidin-1-yl or piperazin-1-yl optionally substituted with one or two $R^b$ independently selected from hydrogen, methyl, trifluoromethyl, methoxy, hydroxy, trifluoromethoxy, carboxy, fluoro, or methoxycarbonyl and one $R^c$ selected from hydroxymethyl, hydroxyethyl, 2-or 3-hydroxypropyl, 2-dimethylaminoethyl, phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, cyclopropyl, cyclopropylmethyl, benzoyl, pyridinylcarbonyl, benzyloxycarbonyl, cyclopropyloxycarbonyl, tetrahydropyran-4-yloxycarbonyl, methylaminocarbonyl, or dimethylaminocarbonyl; and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from methyl, ethyl, trifluoromethyl, methoxy, hydroxyl, ethoxy, trifluoromethoxy, or fluoro. More preferably, $R^5$ and $R^6$ together with the nitrogen atom to which they are attached forms piperazin-1-yl or piperidin-1-yl which is substituted at the 4-position with an $R^c$ group (generic and specific) listed in (c) above.

(d) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form a bridged azabicyclic ring optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, acyl, acylalkyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, heterocycloalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, aminosulfonyl, or $–SO_2R^{11}$ (where

$R^{11}$ is alkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; provided that the heterocycloamino ring is substituted with at least an $R^c$ provided that (a) $R^c$ is not an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$.

(e) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano. Preferably, $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form 2,3-dihydroindol-1-yl, 3,4-dihydroisoquinolin-2-yl, morpholinyl, piperidin-1-yl, or piperazin-1-yl optionally substituted with one, two, or three $R^a$ independently selected from methyl, ethyl, trifluoromethyl, methoxy, hydroxyl, ethoxy, trifluoromethoxy, or fluoro.

(f) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, acyl, or alkoxycarbonyl; and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo. Preferably, $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form 2,3-dihydroindol-1-yl, 3,4-dihydroisoquinolin-2-yl, morpholinyl, piperidin-1-yl or piperazin-1-yl optionally substituted with with one or two $R^b$ independently selected from hydrogen, methyl, trifluoromethyl, methoxy, hydroxyl, trifluoromethoxy, carboxy, fluoro, or methoxycarbonyl and one $R^c$ selected from phenyl, pyridinyl, pyrimidinyl, benzyl, cyclopropyl, cyclopropylmethyl, benzoyl, acetyl, or trifluoroacetyl; and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted

with one, two, or three $R^q$ independently selected from methyl, ethyl, trifluoromethyl, methoxy, hydroxyl, ethoxy, trifluoromethoxy, or fluoro.

(g) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^6$ is methyl or ethyl and $R^5$ is 2-imidazol-4-ylethyl, imidazol-4-ylmethyl, 1-methylimidazol-4-ylmethyl, 2-(1-methylimidazol-4-yl)ethyl, 4-$CF_3$pyridin-3-yl, 4-CNpyridin-3-yl, 3-$CF_3$pyridin-2-yl, 3-CNpyridin-2-yl, 3-$CF_3$pyridin-4-yl, 3-CNpyridin-4-yl, 2-$CF_3$pyridin-3-yl, 2-CNpyridin-3-yl, 2- *N*-methylaminoethyl, 2-*N*,*N*-dimethylaminoethyl, 2-*N*-ethyl-*N*-methylaminoethyl, 2-*N*-isopropyl-*N*-methylaminoethyl, 2-(*N* –cyclopropyl-*N*-methylamino)ethyl, 2-(*N*-cyclobutyl-*N*-methylamino)ethyl, 2-[*N*-(oxetan-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(azetidin-3-yl)-*N*-methylamino]ethyl, 2-[ *N*-(1,1-dioxo-1$\lambda^6$-thietan-3-yl)methylamino]ethyl, 2-(*N*-cyclopentyl-*N*-methylamino)ethyl, 2-[*N*-(3-$CH_3O$cyclopentyl)-*N*-methylamino]ethyl, 2-[*N*-(3-$CHF_2O$cyclopentyl)-*N*-methylamino]ethyl, 2-[*N*-(3-$CF_3O$cyclopentyl)-*N*-methylamino]ethyl, 2-[*N*-(3-phenoxycyclopentyl)-*N*-methylamino)ethyl, 2-{*N*-[3-(4-Fphenoxy)cyclopentyl]-*N*-methylamino}ethyl, 2-{*N*-[3-(4-Clphenoxy)cyclopentyl]-*N*-methylamino}ethyl, 2-{*N*-[3-(4-Brphenoxy)cyclopentyl]-*N*-methylamino}ethyl, 2-{*N*-[3-(4-COOH-phenoxy)cyclopentyl]-*N*-methylamino}ethyl, 2-{*N*-[3-(4-CN-phenoxy)cyclopentyl]-*N*-methylamino}ethyl, 2-{*N*-[3-(4-$CONH_2$-phenoxy)cyclopentyl]-*N*-methylamino}ethyl, 2-(*N*-cyclohexyl-*N*-methylamino)ethyl, 2-[*N*-(tetrahydropyran-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(piperidin-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(1-acetylpiperidin-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(1-$CF_3CO$piperidin-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(tetrahydrothiopyran-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(1-$CH_3SO_2$piperidin-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(tetrahydropyran-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(tetrahydrothiopyran-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(piperidin-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(1-$CH_3CO$piperidin-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(1-$CF_3CO$piperidin-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(1-$CH_3SO_2$piperidin-3-yl)-*N*-methylamino]ethyl, 2-(*N*-$CH_3SO_2$-*N*-methylamino)ethyl, 2-(*N*-$CF_3SO_2$-*N*-methylamino)ethyl, 2-(*N*-$C_2H_5SO_2$-*N*-methylamino)ethyl, 2-[*N*-$(CH_3)_2CHSO_2$-*N*-methylamino]ethyl, 2-(*N*-cyclopropyl$SO_2$-*N*-methylamino)ethyl, 2-(*N*-cyclobutyl$SO_2$-*N*-methylamino)ethyl, 2-(*N*-cyclopentyl$SO_2$-*N*-methylamino)ethyl, 2-(*N*-cyclohexyl$SO_2$-*N*-methylamino)ethyl, 2-(*N*-phenyl$SO_2$-*N*-methylamino)ethyl, 2-[*N*-(2-$CH_3$phenyl$SO_2$)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$phenyl$SO_2$)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$phenyl$SO_2$)-*N*-

methylamino]ethyl, 2-[*N*-(2-FphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(3-FphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(4-FphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(2-OHphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(3-OHphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(4-OHphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(2-CH$_3$OphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(3-CH$_3$OphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(4-CH$_3$OphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(2-CO$_2$HphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(3-CO$_2$HphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(4-CO$_2$HphenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(2-CONH$_2$phenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(3-CONH$_2$phenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(4-CONH$_2$phenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(2-CON(CH$_3$)$_2$phenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(3-CON(CH$_3$)$_2$phenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(4-CON(CH$_3$)$_2$phenylSO$_2$)-*N*-methylamino]ethyl, 2-[*N*-(methylphenylaminocarbonyl)-*N*-methylamino]ethyl, 2-{*N*-[(3-CONH$_2$phenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(4-CONH$_2$phenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(2-CONH$_2$phenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(3-Fphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(4-Fphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(2-Fphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(2-CH$_3$Ophenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(3-CNphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(4-CNphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(2-CNphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(3-OHphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(4-OHphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(2-OHphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(3-CH$_3$Ophenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(4-CH$_3$Ophenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(pyridin-2-yl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(pyridin-3-yl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(pyridin-4-yl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(pyrimidin-2-yl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(pyrimidin-4-yl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(pyrimidin-5yl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[([1.3.5]-triazin-2-yl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(3-CO$_2$Hphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(4-CO$_2$Hphenyl)methylNCO]-*N*-methylamino}ethyl, 2-{*N*-[(2-CO$_2$Hphenyl)methylNCO]-*N*-methylamino}ethyl, 2-(*N*-CH$_3$OCO-*N*-methylamino)ethyl, 2-(*N*-C$_2$H$_5$OCO-*N*-methylamino)ethyl, 2-[*N*-(CH$_3$)$_2$CHOCO-*N*-methylamino]ethyl, 2-[*N*-(CH$_3$)$_3$COCO-*N*-methylamino]ethyl, 2-(*N*-cyclopropylOCO-*N*-methylamino)ethyl, 2-(*N*-cyclobutylOCO-*N*-methylamino)ethyl, 2-[*N*-(oxetan-3-ylOCO)-*N*-methylamino]ethyl, 2-[*N*-(1-acetylazetidin-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(CF$_3$COazetidin-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(1-CH$_3$SO$_2$azetidin-3-yl)-*N*-methylamino]ethyl, 2-[ *N*-(1,1-dioxo-1$\lambda^6$-thietan-3-ylOCO)methylamino]ethyl, 2-[ *N*-(tetrahydrofuran-3-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-

(tetrahydrothiophen-3-ylOCO)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-tetrahydrothiophen-3-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(pyrrolidin-3-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(1-$CH_3$COpyrrolidin-3-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(1-$CF_3$COpyrrolidin-3-ylOCO)-methylamino]ethyl, 2-[ *N*-(1-$CH_3SO_2$pyrrolidin-3-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(cyclohexylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(tetrahydropyran-4-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(tetrahydrothiopyran-4-ylOCO)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-3-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(piperidin-4-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(1-$CH_3$COpiperidin-4-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(1-$CF_3$COpiperidin-4-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(1-$CH_3SO_2$piperidin-4-ylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(benzylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(2-$CH_3$phenylmethyl-OCO)-*N*-methylamino]ethyl, 2-[ *N*-(3-$CH_3$phenylmethylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(4-$CH_3$phenylmethylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(2-Fphenylmethyl OCO)-*N*-methylamino]ethyl, 2-[ *N*-(3-FphenylmethylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(4-Fphenyl-methylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(2-OHphenylmethyl OCO)-*N*-methylamino]ethyl, 2-[ *N*-(3-OHphenylmethylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(4-OHphenylmethylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(2-$CH_3$Ophenylmethylocco)-*N*-methylamino]ethyl, 2-[ *N*-(3-$CH_3$Ophenylmethylocco)-*N*-methylamino]ethyl, 2-[ *N*-(4-$CH_3$Ophenylmethylocco)-*N*-methylamino]ethyl, 2-[ *N*-(2-CNphenylmethyl OCO)-*N*-methylamino]ethyl, 2-[ *N*-(3-CNphenylmethylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(4-CNphenylmethylOCO)-*N*-methylamino]ethyl, 2-[ *N*-(2-$CO_2$Hphenylmethylocco)-*N*-methylamino]ethyl, 2-[ *N*-(3-$CO_2$Hphenylmethylocco)-*N*-methylamino]ethyl, 2-[*N*-(4-$CO_2$Hphenylmethylocco)-*N*-methylamino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethylocco)-*N*-methylamino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethylocco)-*N*-methylamino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethylocco)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-2-ylmethyl OCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-3-ylmethylOCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-4-ylmethylOCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-2-ylmethyl OCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-4-ylmethylOCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-5-ylmethylOCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrazin-2-ylmethyl OCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridazin-3-ylmethylOCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridazin-4-ylmethylOCO)-*N*-methylamino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylmethyl OCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3$phenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$phenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$phenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-FphenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-FphenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-FphenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-OHphenylmethylNHCO) -*N*-methylamino]ethyl, 2-[*N*-(3-

OHphenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-OHphenylmethylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3$Ophenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$Ophenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$Ophenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(2-CNphenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(3-CNphenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(4-CNphenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(2-$CO_2$Hphenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(3-$CO_2$Hphenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(4-$CO_2$Hphenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-2-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-3-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-4-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-2-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-4-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-5-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyrazin-2-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyridazin-3-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(pyridazin-4-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylmethylnhco)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3$phenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$phenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$phenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(2-Fphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(3-Fphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(4-Fphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(2-OHphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(3-OHphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(4-OHphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3$Ophenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$Ophenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$Ophenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(2-CNphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(3-CNphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(4-CNphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(2-$CO_2$Hphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(3-$CO_2$Hphenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(4-$CO_2$Hphenylmethyln($CH_3$)co) -*N*-methylamino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethyl-N($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethyln($CH_3$)co)-*N*-methyl-amino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-2-ylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-3-ylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-4-ylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-2-ylmethyln($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-4-ylmethyl-N($CH_3$)co)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-5-ylmethyln($CH_3$)co)-*N*-methyl-

amino]ethyl, 2-[*N*-(pyrazin-2-ylmethylN($CH_3$)CO)-*N*-methylamino]ethyl, 2-[*N*-(pyridazin-3-ylmethylN($CH_3$)CO)-*N*-methylamino]ethyl, 2-[*N*-(pyridazin-4-ylmethylN($CH_3$)CO) *N*-methylamino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylmethyl-*N*-($CH_3$)CO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-3-yl)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-2-yl)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-2-yl)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-5-yl)-*N*-methylamino]ethyl, 2-[*N*-([1.3.5]triazin-2-yl)-*N*-methylamino]ethyl, 2-[*N*-(phenyl)-*N*-methylamino]ethyl, 2-[*N*-(pyrazin-2-yl)-*N*-methyl-amino]ethyl, 2-[*N*-(pyridazin-4-yl)-*N*-methylamino]ethyl, 2-[*N*-(pyridazin-3-yl)-*N*-methyl-amino]ethyl, 2-[*N*-(4-F-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(3-F-phenyl)-*N*-methylamino]ethyl 2-[*N*-(2-F-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2,4-diF-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2,3-diF-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2,5-diF-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2,6-diF-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2,4,6-triF-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2,3,6-triF-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2,3,4-triF-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3O$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3O$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3O$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(4-CN-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(3-CN-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2-CN-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(4-$CO_2H$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(3-$CO_2H$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2-$CO_2H$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(4-$CONH_2$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(3-$CONH_2$-phenyl)-*N*-methylamino]ethyl, 2-[*N*-(2-$CONH_2$-phenyl)-*N*-methylamino]ethyl, 2-(*N*-$CH_3CO$-*N*-methylamino)ethyl, 2-(*N*-$CF_3CO$-*N*-methylamino)ethyl, 2-(*N*-$C_2H_5CO$-*N*-methylamino)ethyl, 2-[*N*-$(CH_3)_2CHCO$-*N*-methylamino]ethyl, 2-[*N*-$(CH_3)_3CCO$-*N*-methylamino]ethyl, 2-(*N*-cyclopropylCO-*N*-methylamino)ethyl, 2-(*N*-cyclobutylCO-*N*-methylamino)ethyl, 2-[*N*-(oxetan-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(azetidin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-tetrahydrothiophen-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(azetidin-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1-acetylazetidin-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-($CF_3$COazetidin-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1-$CH_3SO_2$azetidin-3-ylCO)-*N*-methylamino]ethyl, 2-(*N*-cyclopentylCO-*N*-methylamino)ethyl, 2-[*N*-(3-$CH_3O$pyrrolidin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CF_3O$pyrrolidin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CHF_2O$pyrrolidin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-phenoxypyrrolidin-1-ylCO)-*N*-methylamino]ethyl, 2-{*N*-[3-(4-Fphenoxy)pyrrolidin-1-ylCO]-*N*-methylamino}ethyl, 2-{*N*-[3-(4-Clphenoxy)pyrrolidin-1-ylCO]-*N*-methylamino}ethyl, 2-{*N*-[3-(4-Brphenoxy)pyrrolidin-1-ylCO]-*N*-methylamino}ethyl, 2-{*N*-[3-(COOH-pyrrolidin-1-ylCO]-*N*-methylamino}ethyl, 2-{*N*-[3-(CN-pyrrolidin-1-ylCO]-*N*-methylamino}ethyl, 2-{*N*-[3-($CONH_2$-phenoxy)cyclopentylCO]-*N*-methylamino}ethyl, 2-{*N*-[3-($CONHCH_3$-pyrrolidin-1-

ylCO]-*N*-methylamino}ethyl, 2-{*N*-[3-(CON($CH_3$)$_2$-pyrrolidin-1-ylCO]-*N*-methylamino}ethyl 2-[*N*-(pyrrolidin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(morpholin-4-ylCO)-*N*-methylamino]-ethyl, 2-[*N*-(1-oxazolidin-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(tetrahydrofuran-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(tetrahydrothiophen-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-tetrahydrothiophen-3-ylCO)-*N*-methylamino]ethyl, 2-(*N*-cyclohexylCO-*N*-methylamino)-ethyl, 2-[*N*-(tetrahydropyran-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(piperidin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1-$CH_3$COpiperidin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1-$CF_3$COpiperidin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1-$CH_3SO_2$piperidin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(tetrahydrothiopyran-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(piperidin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(thiomorpholin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1,1-dioxothiomorpholin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(piperazin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$COpiperazin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CF_3$COpiperazin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-($CH_3SO_2$piperazin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(phenylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-FphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-FphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-FphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-OHphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-OHphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-OHphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3$OphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$OphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$OphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CO_2$HphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CO_2$HphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CO_2$HphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-CNphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-CNphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-CNphenylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3$phenylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$phenylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3$phenylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CONH_2$phenylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CONH_2$phenylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CONH_2$phenylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-2-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-3-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-4-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-2-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-5-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(benzylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-FphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-FphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-FphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CH_3$OphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3$OphenylmethylCO)-*N*-

methylamino]ethyl, 2-[*N*-(4-$CH_3O$phenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-CNphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-CNphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-CNphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-OHphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-OHphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-OHphenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CO_2H$phenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CO_2H$phenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CO_2H$phenylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-2-ylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-3-ylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-4-ylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-2-ylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-4-ylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-5-ylmethylCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrazin-2-ylmethylCO)-*N*-methylamino]ethyl 2-[*N*-(phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CONH_2$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CONH_2$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CONH_2$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-FphenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-FphenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-FphenylNHCO)-*N*-methylamino]ethyl, , 2-[*N*-(2-$CH_3O$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CH_3O$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CH_3O$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-CNphenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-CNphenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-CNphenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-OHphenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-OHphenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-OHphenyl-NHCO)-*N*-methylamino]ethyl, 2-[*N*-(2-$CO_2H$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(3-$CO_2H$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(4-$CO_2H$phenylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-2-ylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-3-ylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(pyridin-4-ylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-2-ylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-4-ylNHCO)-*N*-methylamino]ethyl, 2-[*N*-(pyrimidin-5-ylNHCO)-*N*-methylamino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylNHCO)-*N*-methylamino]ethyl, 2-[ *N*-(1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(8-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-F-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-F-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(8-F-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-$CH_3O$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-$CH_3O$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(8-$CH_3O$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-

methylamino]ethyl, 2-[*N*-(7-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(8-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(8-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-$CO_2H$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-$CO_2H$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(8-$CO_2H$-1,2,3,4-tetrahydroquinolin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1,2,3,4-tetrahydro-[1,8]naphthyridin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1,2,3,4-tetrahydro-[1,7]naphthyridin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(1,2,3,4-tetrahydro-[1,6]naphthyridin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-5-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-8-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[3,2-d]pyrimidin-5-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[2,3-d]pyridazin-1-ylCO)-*N*-methylamino]ethyl, 2-[ *N*-(2,3-dihydro-1*H*-indol-1-ylCO)methylamino]ethyl, 2-[*N*-(7-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]-ethyl, 2-[*N*-(6-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-F-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-F-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5-F-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-$CH_3O$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-$CH_3O$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methyl-amino]ethyl, 2-[*N*-(5-$CH_3O$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-CN-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-CN-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5-CN-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-OH-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-OH-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5-OH-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(7-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(5-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6,7-dihydro-51H-pyrrolo[2,3-b]pyrazin-5-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-7-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(6,7-dihydro-5H-pyrrolo[3,2-d]pyrimidin-5-ylCO)-*N*-methylamino]ethyl, 2-[*N*-(2,3-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-ylCO)-*N*-methylamino]ethyl, 2-aminoethyl, 2-*N*-methylaminoethyl

2-*N*-ethylaminoethyl, 2-(2,2,2-trifluoroethylamino)ethyl, 2-*N*-isopropylaminoethyl, 2-[2-$CF_3$-2,2,2-trifluoroethylamino)ethyl, 2-(*N*–cyclopropylamino)ethyl, 2-(*N*-cyclobutylamino)ethyl, 2-[*N*-(oxetan-3-yl)amino]ethyl, 2-[*N*-(azetidin-3-yl)amino]ethyl, 2-[ *N*-(1,1-dioxo-1$\lambda^6$-thietan-3-yl)amino]ethyl, 2-(*N*-cyclopentylamino)ethyl, 2-[*N*-(3-$CH_3O$cyclopentyl)amino]ethyl, 2-[*N*-(3-$CHF_2O$cyclopentyl)amino]ethyl, 2-[*N*-(3-$CF_3O$cyclopentyl)amino]ethyl, 2-[*N*-(3-phenoxy-cyclopentyl)amino)ethyl, 2-{*N*-[3-(4-Fphenoxy)cyclopentyl]amino}ethyl, 2-{*N*-[3-(4-Clphenoxy)cyclopentyl]amino}ethyl, 2-{*N*-[3-(4-Brphenoxy)cyclopentyl]amino}ethyl, 2-{*N*-[3-(COOH-phenoxy)cyclopentyl]amino}ethyl, 2-{*N*-[3-(CN-phenoxy)cyclopentyl]amino}ethyl, 2-{*N*-[3-($CONH_2$-phenoxy)cyclopentyl]amino}ethyl, 2-(*N*-cyclohexylamino)ethyl, 2-[*N*-(tetrahydropyran-4-yl)amino]ethyl, 2-[*N*-(piperidin-4-yl)amino]ethyl, 2-[*N*-(1-acetylpiperidin-4-yl)amino]ethyl, 2-[*N*-(1-$CF_3CO$piperidin-4-yl)amino]ethyl, 2-[*N*-(tetrahydrothiopyran-4-yl)amino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-4-yl)amino]ethyl, 2-[*N*-(1-$CH_3SO_2$piperidin-4-yl)amino]ethyl, 2-[*N*-(tetrahydropyran-3-yl)amino]ethyl, 2-[*N*-(tetrahydrothiopyran-3-yl)amino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-3-yl)amino]ethyl, 2-[*N*-(piperidin-3-yl)amino]ethyl, 2-[*N*-(1-$CH_3CO$piperidin-3-yl)amino]ethyl, 2-[*N*-(1-$CF_3CO$piperidin-3-yl)amino]ethyl, 2-[*N*-(1-$CH_3SO_2$piperidin-3-yl)amino]ethyl, 2-(*N*-$CH_3SO_2$amino)ethyl, 2-(*N*-$CF_3SO_2$amino)ethyl, 2-(*N*-$C_2H_5SO_2$amino)ethyl, 2-[*N*-$(CH_3)_2CHSO_2$amino]ethyl, 2-[*N*-$(CH_3)_3CSO_2$amino]ethyl, 2-(*N*-cyclopropyl$SO_2$amino)ethyl, 2-(*N*-cyclobutyl$SO_2$amino)ethyl, 2-(*N*-cyclopentyl$SO_2$amino)ethyl, 2-(*N*-cyclohexyl$SO_2$-amino)ethyl, 2-(*N*-phenylamino)ethyl, 2-[*N*-(2-$CH_3$phenyl$SO_2$)amino]ethyl, 2-[*N*-(3-$CH_3$phenyl$SO_2$)amino]ethyl, 2-[*N*-(4-$CH_3$phenyl$SO_2$)amino]ethyl, 2-[*N*-(2-Fphenyl$SO_2$)-amino]ethyl, 2-[*N*-(3-Fphenyl$SO_2$)amino]ethyl, 2-[*N*-(4-Fphenyl$SO_2$)amino]ethyl, 2-[*N*-(2-OHphenyl$SO_2$)amino]ethyl, 2-[*N*-(3-OHphenyl$SO_2$)amino]ethyl, 2-[*N*-(4-OHphenyl$SO_2$)-amino]ethyl, 2-[*N*-(2-$CH_3O$phenyl$SO_2$)amino]ethyl, 2-[*N*-(3-$CH_3O$phenyl$SO_2$)amino]ethyl, 2-[*N*-(4-$CH_3O$phenyl$SO_2$)amino]ethyl, 2-[*N*-(2-$CO_2H$phenyl$SO_2$)amino]ethyl, 2-[*N*-(3-$CO_2H$phenyl$SO_2$)amino]ethyl, 2-[*N*-(4-$CO_2H$phenyl$SO_2$)amino]ethyl, 2-[*N*-(2-$CONH_2$phenyl-$SO_2$)amino]ethyl, 2-[*N*-(3-$CONH_2$phenyl$SO_2$)amino]ethyl, 2-[*N*-(4-$CONH_2$phenyl$SO_2$)-amino]ethyl, 2-[*N*-(2-$CON(CH_3)_2$phenyl$SO_2$)amino]ethyl, 2-[*N*-(3-$CON(CH_3)_2$phenyl$SO_2$)-amino]ethyl, 2-[*N*-(4-$CON(CH_3)_2$phenyl$SO_2$)amino]ethyl, 2-[*N*-(methylphenylaminocarbonyl)-amino]ethyl, 2-{*N*-[(3-$CONH_2$phenyl)methylNCO]amino}ethyl, 2-{*N*-[(4-$CONH_2$phenyl)-methylNCO]amino}ethyl, 2-{*N*-[(2-$CONH_2$phenyl)methylNCO]amino}ethyl, 2-{*N*-[(3-Fphenyl)methylNCO]amino}ethyl, 2-{*N*-[(4-Fphenyl)methylNCO]amino}ethyl, 2-{*N*-[(2-Fphenyl)methylNCO]amino}ethyl, 2-{*N*-[(2-$CH_3O$phenyl)methylNCO]amino}ethyl, 2-{*N*-[(3-CNphenyl)methylNCO]amino}ethyl, 2-{*N*-[(4-CNphenyl)methylNCO]amino}ethyl, 2-{*N*-[(2-

CNphenyl)methylNCO]amino}ethyl, 2-{*N*-[(3-OHphenyl)methylNCO]amino}ethyl, 2-{*N*-[(4-OHphenyl)methylNCO]amino}ethyl, 2-{*N*-[(2-OHphenyl)methylNCO]amino}ethyl, 2-{*N*-[(3-$CH_3O$phenyl)methylNCO]amino}ethyl, 2-{*N*-[(4-$CH_3O$phenyl)methylNCO]amino}ethyl, 2-{*N*-[(pyridin-2-yl)methylNCO]amino}ethyl, 2-{*N*-[(pyridin-3-yl)methylNCO]amino}ethyl, 2-{*N*-[(pyridin-4-yl)methylNCO]amino}ethyl, 2-{*N*-[(pyrimidin-2-yl)methylNCO]amino}ethyl, 2-{*N*-[(pyrimidin-4-yl)methylNCO]amino}ethyl, 2-{*N*-[(pyrimidin-5yl)methylNCO]amino}ethyl, 2-{*N*-[([1.3.5]-triazin-2-yl)methylNCO]amino}ethyl, 2-{*N*-[(3-$CO_2H$phenyl)methyl-NCO]amino}ethyl, 2-{*N*-[(4-$CO_2H$phenyl)methylNCO]amino}ethyl, 2-{*N*-[(2-$CO_2H$phenyl)methylNCO]amino}ethyl, 2-(*N*-$CH_3OCO$amino)ethyl, 2-(*N*-$C_2H_5OCO$amino)ethyl 2-[*N*-$(CH_3)_2CHOCO$amino]ethyl, 2-[*N*-$(CH_3)_3COCO$amino]ethyl, 2-(*N*-cyclopropylOCO-amino)ethyl, 2-(*N*-cyclobutylOCOamino)ethyl, 2-[*N*-(oxetan-3-ylOCO) amino]ethyl, 2-[*N*-(azetidin-3-yl)amino]ethyl, 2-[*N*-(1-acetylazetidin-3-yl)amino]ethyl, 2-[*N*-($CF_3CO$azetidin-3-yl)amino]ethyl, 2-[*N*-(1-$CH_3SO_2$azetidin-3-yl)amino]ethyl, 2-[ *N*-(1,1-dioxo-1$\lambda^6$-thietan-3-ylOCO)amino]ethyl, 2-[ *N*-(tetrahydrofuran-3-ylOCO)amino]ethyl, 2-[ *N*-(tetrahydrothiophen-3-ylOCO)amino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-tetrahydrothiophen-3-ylOCO)amino]ethyl 2-[ *N*-(pyrrolidin-3-ylOCO)amino]ethyl, 2-[ *N*-(1-$CH_3CO$pyrrolidin-3-ylOCO)amino]ethyl 2-[ *N*-(1-$CF_3CO$pyrrolidin-3-ylOCO)amino]ethyl, 2-[ *N*-(1-$CH_3SO_2$pyrrolidin-3-ylOCO)amino]ethyl, 2-[ *N*-(cyclohexylOCO)amino]ethyl, 2-[ *N*-(tetrahydropyran-4-ylOCO)amino]ethyl, 2-[ *N*-(tetrahydrothiopyran-4-ylOCO)amino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-3-ylOCO)-amino]ethyl, 2-[ *N*-(piperidin-4-ylOCO)amino]ethyl, 2-[ *N*-(1-$CH_3CO$piperidin-4-ylOCO)amino]ethyl, 2-[ *N*-(1-$CF_3CO$piperidin-4-ylOCO)amino]ethyl, 2-[ *N*-(1-$CH_3SO_2$piperidin-4-ylOCO)amino]ethyl, 2-[ *N*-(benzylOCO)amino]ethyl, 2-[ *N*-(2-$CH_3$phenylmethylOCO)amino]ethyl, 2-[ *N*-(3-$CH_3$phenylmethylOCO)amino]ethyl, 2-[ *N*-(4-$CH_3$phenylmethylOCO)amino]ethyl, 2-[ *N*-(2-Fphenylmethyl OCO)amino]ethyl, 2-[ *N*-(3-FphenylmethylOCO)amino]ethyl, 2-[ *N*-(4-FphenylmethylOCO)amino]ethyl, 2-[ *N*-(2-OHphenylmethyl OCO)amino]ethyl, 2-[ *N*-(3-OHphenylmethylOCO)amino]ethyl, 2-[ *N*-(4-OHphenylmethylOCO)amino]ethyl, 2-[ *N*-(2-$CH_3O$phenylmethylOCO)amino]ethyl, 2-[ *N*-(3-$CH_3O$phenylmethylOCO)amino]ethyl, 2-[ *N*-(4-$CH_3O$phenylmethylOCO)amino]ethyl, 2-[ *N*-(2-CNphenylmethyl OCO)amino]ethyl, 2-[ *N*-(3-CNphenylmethylOCO)amino]ethyl, 2-[ *N*-(4-CNphenylmethylOCO)amino]ethyl, 2-[ *N*-(2-$CO_2H$phenylmethylOCO)amino]ethyl, 2-[ *N*-(3-$CO_2H$phenylmethylOCO)amino]ethyl, 2-[*N*-(4-$CO_2H$phenylmethylOCO)amino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethylOCO)amino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethylOCO)amino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethylOCO)amino]ethyl, 2-[*N*-(pyridin-2-ylmethyl OCO)amino]ethyl, 2-[*N*-(pyridin-3-ylmethylOCO)amino]ethyl, 2-[*N*-(pyridin-4-ylmethylOCO)amino]ethyl, 2-[*N*-

(pyrimidin-2-ylmethyl OCO)amino]ethyl, 2-[*N*-(pyrimidin-4-ylmethylOCO)amino]ethyl, 2-[*N*-(pyrimidin-5-ylmethylOCO)amino]ethyl, 2-[*N*-(pyrazin-2-ylmethyl OCO)amino]ethyl, 2-[*N*-(pyridazin-3-ylmethylOCO)amino]ethyl, 2-[*N*-(pyridazin-4-ylmethylOCO)amino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylmethyl OCO)amino]ethyl, 2-[*N*-(2-$CH_3$phenylmethylNHCO)amino]ethyl, 2-[*N*-(3-$CH_3$phenylmethylNHCO)amino]ethyl, 2-[*N*-(4-$CH_3$phenylmethylNHCO)amino]ethyl, 2-[*N*-(2-FphenylmethylNHCO)amino]ethyl, 2-[*N*-(3-FphenylmethylNHCO)amino]ethyl, 2-[*N*-(4-FphenylmethylNHCO)amino]ethyl, 2-[*N*-(2-OHphenylmethylNHCO)amino]ethyl, 2-[*N*-(3-OHphenylmethylNHCO)amino]ethyl, 2-[*N*-(4-OHphenylmethylNHCO)amino]ethyl, 2-[*N*-(2-$CH_3$OphenylmethylNHCO)amino]ethyl, 2-[*N*-(3-$CH_3$OphenylmethylNHCO)amino]ethyl, 2-[*N*-(4-$CH_3$OphenylmethylNHCO) amino]ethyl, 2-[*N*-(2-CNphenylmethylNHCO) amino]ethyl, 2-[*N*-(3-CNphenylmethylNHCO)amino]ethyl, 2-[*N*-(4-CNphenylmethylNHCO)amino]ethyl, 2-[*N*-(2-$CO_2$Hphenylmethyl NHCO)amino]ethyl, 2-[*N*-(3-$CO_2$Hphenylmethyl NHCO)amino]ethyl, 2-[*N*-(4-$CO_2$Hphenylmethyl NHCO)amino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethylNHCO)-amino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethylNHCO)amino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethyl-NHCO)amino]ethyl, 2-[*N*-(pyridin-2-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyridin-3-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyridin-4-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyrimidin-2-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyrimidin-4-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyrimidin-5-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyrazin-2-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyridazin-3-ylmethylNHCO)amino]ethyl, 2-[*N*-(pyridazin-4-ylmethylNHCO)amino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylmethylNHCO)amino]ethyl, 2-[*N*-(2-$CH_3$phenylmethylN($CH_3$)CO)-amino]ethyl, 2-[*N*-(3-$CH_3$phenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(4-$CH_3$phenylmethyl-N($CH_3$)CO)amino]ethyl, 2-[*N*-(2-FphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(3-FphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(4-FphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(2-OHphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(3-OHphenylmethylN($CH_3$)CO)-amino]ethyl, 2-[*N*-(4-OHphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(2-$CH_3$Ophenylmethyl-N($CH_3$)CO)amino]ethyl, 2-[*N*-(3-$CH_3$OphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(4-$CH_3$OphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(2-CNphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(3-CNphenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(4-CNphenylmethylN($CH_3$)CO)-amino]ethyl, 2-[*N*-(2-$CO_2$Hphenylmethyl N($CH_3$)CO)amino]ethyl, 2-[*N*-(3-$CO_2$Hphenylmethyl-N($CH_3$)CO)amino]ethyl, 2-[*N*-(4-$CO_2$Hphenylmethyl N($CH_3$)CO)amino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethylN($CH_3$)CO)-amino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyridin-2-ylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyridin-3-ylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyridin-4-ylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyrimidin-2-ylmethylN($CH_3$)CO)-

amino]ethyl, 2-[*N*-(pyrimidin-4-ylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyrimidin-5-ylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyrazin-2-ylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyridazin-3-ylmethylN($CH_3$)CO)amino]ethyl, 2-[*N*-(pyridazin-4-ylmethylN($CH_3$)CO)-amino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylmethyl*N*($CH_3$)CO)amino]ethyl, 2-[*N*-(pyridin-4-yl)amino]ethyl, 2-[*N*-(pyridin-3-yl)amino]ethyl, 2-[*N*-(pyridin-2-yl)amino]ethyl, 2-[*N*-(pyrimidin-4-yl)amino]ethyl, 2-[*N*-(pyrimidin-2-yl)amino]ethyl, 2-[*N*-(pyrimidin-5-yl)amino]ethyl, 2-[*N*-([1.3.5]triazin-2-yl)amino]ethyl, 2-[*N*-(phenyl)amino]ethyl, 2-[*N*-(pyrazin-2-yl)amino]ethyl, 2-[*N*-(pyridazin-4-yl)amino]ethyl, 2-[*N*-(pyridazin-3-yl)amino]ethyl, 2-[*N*-(4-F-phenyl)amino]ethyl, 2-[*N*-(3-F-phenyl)amino]ethyl, 2-[*N*-(2-F-phenyl)amino]ethyl, 2-[*N*-(2,4-diF-phenyl)amino]ethyl, 2-[*N*-(2,3-diF-phenyl)amino]ethyl, 2-[*N*-(2,5-diF-phenyl)amino]ethyl, 2-[*N*-(2,6-diF-phenyl)amino]ethyl, 2-[*N*-(2,4,6-triF-phenyl)amino]ethyl, 2-[*N*-(2,3,6-triF-phenyl)amino]ethyl, 2-[*N*-(2,3,4-triF-phenyl)amino]ethyl, 2-[*N*-(4-$CH_3O$-phenyl)amino]ethyl, 2-[*N*-(3-$CH_3O$-phenyl)amino]ethyl, 2-[*N*-(2-$CH_3O$-phenyl)amino]ethyl, 2-[*N*-(4-CN-phenyl)amino]ethyl, 2-[*N*-(3-CN-phenyl)amino]ethyl, 2-[*N*-(2-CN-phenyl)amino]ethyl, 2-[*N*-(4-$CO_2H$-phenyl)amino]ethyl, 2-[*N*-(3-$CO_2H$-phenyl)amino]ethyl, 2-[*N*-(2-$CO_2H$-phenyl)amino]ethyl, 2-[*N*-(4-$CONH_2$-phenyl)amino]ethyl, 2-[*N*-(3-$CONH_2$-phenyl)amino]ethyl 2-[*N*-(2-$CONH_2$-phenyl)amino]ethyl, 2-(*N*-$CH_3$COamino)ethyl, 2-(*N*-$CF_3$COmino)ethyl, 2-(*N*-$C_2H_5$COamino)ethyl, 2-[*N*-$(CH_3)_2$CHCOamino]ethyl, 2-[*N*-$(CH_3)_3$CCOamino]ethyl, 2-(*N*-cyclopropylCOamino)ethyl, 2-(*N*-cyclobutylCOamino)ethyl, 2-[*N*-(oxetan-3-ylCO)amino]ethyl 2-[*N*-(azetidin-1-ylCO)amino]ethyl, 2-[*N*-(1,1-dioxo-1$\lambda^6$-tetrahydrothiophen-3-ylCO)-amino]ethyl, 2-[*N*-(azetidin-3-ylCO)amino]ethyl, 2-[*N*-(1-acetylazetidin-4-ylCO)amino]ethyl, 2-[*N*-($CF_3$COazetidin-4-ylCO)amino]ethyl, 2-[*N*-(1-$CH_3SO_2$azetidin-4-ylCO)amino]ethyl, 2-(*N*-cyclopentylCOamino)ethyl, 2-[*N*-(3-$CH_3$Opyrrolidin-1-ylCO)amino]ethyl, 2-[*N*-(3-$CF_3$Opyrrolidin-1-ylCO)amino]ethyl, 2-[*N*-(3-$CHF_2$Opyrrolidin-1-ylCO)amino]ethyl, 2-[*N*-(3-phenoxypyrrolidin-1-ylCO)amino]ethyl, 2-{*N*-[3-(4-Fphenoxy)pyrrolidin-1-ylCO]amino}ethyl, 2-{*N*-[3-(4-Clphenoxy)pyrrolidin-1-ylCO]amino}ethyl, 2-{*N*-[3-(4-Brphenoxy)pyrrolidin-1-ylCO]amino}ethyl, 2-{*N*-[3-(COOH)pyrrolidin-1-ylCO]amino}ethyl, 2-{*N*-[3-(CN) pyrrolidin-1-ylCO]amino}ethyl, 2-{*N*-[3-($CONH_2$) pyrrolidin-1-ylCO]amino}ethyl, 2-{*N*-[3-($CONHCH_3$) pyrrolidin-1-ylCO]amino}ethyl, 2-{*N*-[3-($CON(CH_3)_2$) pyrrolidin-1-ylCO]amino}ethyl, 2-[*N*-(pyrrolidin-1-ylCO)amino]ethyl, 2-[*N*-(tetrahydrofuran-3-ylCO)amino]ethyl, 2-[*N*-(tetrahydrothiophen-3-ylCO)amino]ethyl, 2-[*N*-(oxazolidin-3-ylCO)amino]ethyl, 2-[*N*-(morpholin-4-yllCO)amino]ethyl, 2-(*N*-cyclopentylCOamino)ethyl, 2-[*N*-(tetrahydropyran-4-ylCO)amino]ethyl, 2-[*N*-(piperidin-4-ylCO)amino]ethyl, 2-[*N*-(1-$CH_3$COpiperidin-4-ylCO)amino]ethyl, 2-[*N*-(1-$CF_3$COpiperidin-4-ylCO)amino]ethyl, 2-[*N*-(1-$CH_3SO_2$piperidin-4-

ylCO)amino]ethyl, 2-[*N*-(tetrahydrothiopyran-4-ylCO)amino]ethyl, 2-[*N*-(1,1-dioxo-1λ°-hexahydrothiopyran-4-ylCO)amino]ethyl, 2-[*N*-(piperidin-1-ylCO)amino]ethyl, 2-[*N*-(thiomorpholin-4-ylCO)amino]ethyl, 2-[*N*-(1,1-dioxothiomorpholin-4-ylCO)amino]ethyl, 2-[*N*-(piperazin-4-ylCO)amino]ethyl, 2-[*N*-(4-$CH_3$COpiperazin-1-ylCO)amino]ethyl, 2-[*N*-(4-$CF_3$COpiperazin-1-ylCO)amino]ethyl, 2-[*N*-($CH_3SO_2$piperazin-1-ylCO)amino]ethyl, 2-[*N*-(phenylCO)amino]ethyl, 2-[*N*-(2-FphenylCO)amino]ethyl, 2-[*N*-(3-FphenylCO)amino]-ethyl, 2-[*N*-(4-FphenylCO)amino]ethyl, 2-[*N*-(2-OHphenylCO)amino]ethyl, 2-[*N*-(3-OHphenylCO)amino]ethyl, 2-[*N*-(4-OHphenylCO)amino]ethyl, 2-[*N*-(2-$CH_3$OphenylCO)-amino]ethyl, 2-[*N*-(3-$CH_3$OphenylCO)amino]ethyl, 2-[*N*-(4-$CH_3$OphenylCO)amino]ethyl, 2-[*N*-(2-$CO_2$HphenylCO)amino]ethyl, 2-[*N*-(3-$CO_2$HphenylCO)amino]ethyl, 2-[*N*-(4-$CO_2$Hphenyl-CO)amino]ethyl, 2-[*N*-(2-CNphenylCO)amino]ethyl, 2-[*N*-(3-CNphenylCO)amino]ethyl, 2-[*N*-(4-CNphenylCO)amino]ethyl, 2-[*N*-(2-$CH_3$phenylCO)amino]ethyl, 2-[*N*-(3-$CH_3$phenylCO)-amino]ethyl, 2-[*N*-(4-$CH_3$phenylCO)amino]ethyl, 2-[*N*-(2-$CONH_2$phenylCO)amino]ethyl, 2-[*N*-(3-$CONH_2$phenylCO)amino]ethyl, 2-[*N*-(4-$CONH_2$phenylCO)amino]ethyl, 2-[*N*-(pyridin-2-ylCO)amino]ethyl, 2-[*N*-(pyridin-3-ylCO)amino]ethyl, 2-[*N*-(pyridin-4-ylCO)amino]ethyl, 2-[*N*-(pyrimidin-4-ylCO)amino]ethyl, 2-[*N*-(pyrimidin-2-ylCO)amino]ethyl, 2-[*N*-(pyrimidin-5-ylCO)amino]ethyl, 2-[ *N*-(benzylCO)amino]ethyl, 2-[*N*-(3-$CONH_2$phenylmethylCO)-amino]ethyl, 2-[*N*-(4-$CONH_2$phenylmethylCO)amino]ethyl, 2-[*N*-(2-$CONH_2$phenylmethylCO)-amino]ethyl, 2-[*N*-(3-FphenylmethylCO)amino]ethyl, 2-[*N*-(4-FphenylmethylCO)amino]ethyl, 2-[*N*-(2-FphenylmethylCO)amino]ethyl, 2-[*N*-(2-$CH_3$OphenylmethylCO)amino]ethyl, 2-[*N*-(3-$CH_3$OphenylmethylCO)amino]ethyl, 2-[*N*-(4-$CH_3$OphenylmethylCO)amino]ethyl, 2-[*N*-(2-CNphenylmethylCO)amino]ethyl, 2-[*N*-(3-CNphenylmethylCO)amino]ethyl, 2-[*N*-(4-CNphenylmethylCO)amino]ethyl, 2-[*N*-(2-OHphenylmethylCO)amino]ethyl, 2-[*N*-(3-OHphenylmethylCO)amino]ethyl, 2-[*N*-(4-OHphenylmethylCO)amino]ethyl, 2-[*N*-(2-$CO_2$HphenylmethylCO)amino]ethyl, 2-[*N*-(3-$CO_2$HphenylmethylCO)amino]ethyl, 2-[*N*-(4-$CO_2$HphenylmethylCO)amino]ethyl, 2-[*N*-(pyridin-2-ylmethylCO)amino]ethyl, 2-[*N*-(pyridin-3-ylmethylCO)amino]ethyl, 2-[*N*-(pyridin-4-ylmethylCO)amino]ethyl, 2-[*N*-(pyrimidin-2-ylmethylCO)amino]ethyl, 2-[*N*-(pyrimidin-4-ylmethylCO)amino]ethyl, 2-[*N*-(pyrimidin-5-ylmethylCO)amino]ethyl, 2-[*N*-(pyrazin-2-ylmethylCO)amino]ethyl, 2-[ *N*-(phenylNHCO)-amino]ethyl, 2-[*N*-(3-$CONH_2$phenylNHCO)amino]ethyl, 2-[*N*-(4-$CONH_2$phenylNHCO)-amino]ethyl, 2-[*N*-(2-$CONH_2$phenylNHCO)amino]ethyl, 2-[*N*-(3-FphenylNHCO)amino]ethyl, 2-[*N*-(4-FphenylNHCO)amino]ethyl, 2-[*N*-(2-FphenylNHCO)amino]ethyl, 2-[*N*-(2-$CH_3$OphenylNHCO)amino]ethyl, 2-[*N*-(3-$CH_3$OphenylNHCO)amino]ethyl, 2-[*N*-(4-$CH_3$OphenylNHCO)amino]ethyl, 2-[*N*-(2-CNphenylNHCO)amino]ethyl, 2-[*N*-(3-

CNphenylNHCO)amino]ethyl, 2-[*N*-(4-CNphenylNHlCO)amino]ethyl, 2-[*N*-(2-OHphenyl-NHCO)amino]ethyl, 2-[*N*-(3-OHphenylNHCO)amino]ethyl, 2-[*N*-(4-OHphenylNHlCO)-amino]ethyl, 2-[*N*-(2-$CO_2$HphenylNHCO)amino]ethyl, 2-[*N*-(3-$CO_2$HphenylNHCO)-amino]ethyl, 2-[*N*-(4-$CO_2$HphenylNHCO)amino]ethyl, 2-[*N*-(pyridin-2-ylNHCO)amino]ethyl, 2-[*N*-(pyridin-3-ylNHlCO)amino]ethyl, 2-[*N*-(pyridin-4-ylNHCO)amino]ethyl, 2-[*N*-(pyrimidin-2-ylNHCO)amino]ethyl, 2-[*N*-(pyrimidin-4-ylNHCO)amino]ethyl, 2-[*N*-(pyrimidin-5-ylNHCO)amino]ethyl, 2-[*N*-([1.3.5]triazin-2-ylNHCO)amino]ethyl, 2-[ *N*-(1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(7-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(6-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(8-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(7-F-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(6-F-1,2,3,4-tetrahydroquinolin-1-ylCO)-amino]ethyl, 2-[*N*-(8-F-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(7-$CH_3O$-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(6-$CH_3O$-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(8-$CH_3O$-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(7-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(6-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(8-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(7-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(6-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(8-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(7-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(6-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(8-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)amino]ethyl, 2-[*N*-(1,2,3,4-tetrahydro-[1,8]naphthyridin-1-ylCO)amino]ethyl, 2-[*N*-(1,2,3,4-tetrahydro-[1,7]naphthyridin-1-ylCO)amino]ethyl, 2-[*N*-(1,2,3,4-tetrahydro-[1,6]naphthyridin-1-ylCO)amino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-5-ylCO)amino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-8-ylCO)amino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[3,2-d]pyrimidin-5-ylCO)amino]ethyl, 2-[*N*-(5,6,7,8-tetrahydropyrido[2,3-d]pyridazin-1-ylCO)amino]ethyl, 2-[ *N*-(2,3-dihydro-1*H*-indol-1-ylCO) amino]ethyl, 2-[*N*-(7-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(6-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(5-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(7-F-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(6-F-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(5-F-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(7-$CH_3O$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(6-$CH_3O$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(5-$CH_3O$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(7-CN-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(6-CN-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(5-CN-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(7-OH-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl,

2-[*N*-(6-OH-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(5-OH-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(7-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(6-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(5-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)amino]ethyl, 2-[*N*-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylCO)-amino]ethyl, 2-[*N*-(2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-1-ylCO)-amino]ethyl, 2-[*N*-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-ylCO)-amino]ethyl, 2-[*N*-(6,7-dihydro-5H-pyrrolo[2,3-b]pyrazin-5-ylCO)-amino]ethyl, 2-[*N*-(6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-7-ylCO)-amino]ethyl 2-[*N*-(6,7-dihydro-5H-pyrrolo[3,2-d]pyrimidin-5-ylCO)-amino]ethyl, or 2-[*N*-(2,3-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-ylCO) amino]ethyl.

(h) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form piperidin-1-yl, 4-methylpiperidin-1-yl, 4-ethylpiperidin-1-yl, 4-(2,2,2-trifluoroethyl)piperidin-1-yl, 4-(2-isopropyl)piperidin-1-yl, 4-(2-trifluoromethyl-2,2,2-trifluoroethyl)piperidin-1-yl 4-(cyclopropyl)piperidin-1-yl, 4-(cyclobutyl)piperidin-1-yl, 4-(oxetan-3-yl)piperidin-1-yl 4-(azetidin-3-yl)piperidin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-thietan-3-yl)piperidin-1-yl, 4-(cyclopentyl)-piperidin-1-yl, 4-(3-$CH_3O$cyclopentyl)piperidin-1-yl, 4-(3-$CHF_2O$cyclopentyl)piperidin-1-yl, 4-(3-$CF_3O$cyclopentyl)piperidin-1-yl, 4-(3-phenoxycyclopentyl)piperidin-1-yl, 4-[3-(4-Fphenoxy)cyclopentyl]piperidin-1-yl, 4-[3-(4-Clphenoxy)cyclopentyl]piperidin-1-yl, 4-[3-(4-Brphenoxy)cyclopentyl]piperidin-1-yl, 4-[3-(4-$CO_2H$phenoxy)cyclopentyl]piperidin-1-yl, 4-[3-(4-CNphenoxy)cyclopentyl]piperidin-1-yl, 4-[3-(4-$CONH_2$phenoxy)cyclopentyl]piperidin-1-yl, 4-(cyclohexyl)piperidin-1-yl, 4-(tetrahydropyran-4-yl)piperidin-1-yl, 4-(piperidin-4-yl)piperidin-1-yl, 4-(tetrahydropyran-3-yl)piperidin-1-yl, 4-(tetrahydrothiopyran-3-yl)piperidin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-3-yl)piperidin-1-yl, 4-(piperidin-3-yl)piperidin-1-yl, 4-(methylsulfonyl)piperidin-1-yl, 4-(ethylsulfonyl)piperidin-1-yl, 4-(isopropylsulfonyl)piperidin-1-yl, 4-(*tert*-butylsulfonyl)piperidin-1-yl, 4-(cyclopropylsulfonyl)piperidin-1-yl, 4-(cyclobutyl-sulfonyl)piperidin-1-yl, 4-(cyclopentylsulfonyl)piperidin-1-yl, 4-(cyclohexylsulfonyl)piperidin-1-yl, 4-(benzenesulfonyl)piperidin-1-yl, 4-(2-$CH_3$phenylsulfonyl)piperidin-1-yl, 4-(3-$CH_3$phenylsulfonyl)piperidin-1-yl, 4-(4-$CH_3$phenylsulfonyl)piperidin-1-yl, 4-(2-Fphenyl-sulfonyl)piperidin-1-yl, 4-(3-Fphenylsulfonyl)piperidin-1-yl, 4-(4-Fphenylsulfonyl)piperidin-1-yl, 4-(2-OHphenylsulfonyl)piperidin-1-yl, 4-(3-OHphenylsulfonyl)piperidin-1-yl, 4-(4-OHphenylsulfonyl)piperidin-1-yl, 4-(2-$CH_3O$phenylsulfonyl)piperidin-1-yl, 4-(3-$CH_3O$phenylsulfonyl)piperidin-1-yl, 4-(4-$CH_3O$phenylsulfonyl)piperidin-1-yl, 4-(2-

$CO_2H$phenylsulfonyl)piperidin-1-yl, 4-(3-$CO_2H$phenylsulfonyl)piperidin-1-yl, 4-(4-$CO_2H$phenylsulfonyl)piperidin-1-yl, 4-(2-$CONH_2$phenylsulfonyl)piperidin-1-yl, 4-(3-$CONH_2$phenylsulfonyl)piperidin-1-yl, 4-(4-$CONH_2$phenylsulfonyl)piperidin-1-yl, 4-(2-$CON(CH_3)_2$phenylsulfonyl)piperidin-1-yl, 4-(3-$CON(CH_3)_2$phenylsulfonyl)piperidin-1-yl, 4-(4-$CON(CH_3)_2$phenylsulfonyl)piperidin-1-yl, 4-(methylphenylNCO)piperidin-1-yl, 4-[(3-$CONH_2$phenyl)methylNCO]piperidin-1-yl, 4-[(4-$CONH_2$phenyl)methylNCO]piperidin-1-yl, 4-[(2-$CONH_2$phenyl)methylNCO]piperidin-1-yl, 4-[(3-Fphenyl)methylNCO]piperidin-1-yl, 4-[(4-Fphenyl)methylNCO]piperidin-1-yl, 4-[(2-Fphenyl)methylNCO]piperidin-1-yl, 4-[(3-$OCH_3$phenyl)methylNCO]piperidin-1-yl, 4-[(4-$OCH_3$phenyl)methylNCO]piperidin-1-yl, 4-[(2-$OCH_3$phenyl)methylNCO]piperidin-1-yl, 4-[(3-CNphenyl)methylNCO]piperidin-1-yl, 4-[(4-CNphenyl)methylNCO]piperidin-1-yl, 4-[(2-CNphenyl)methylNCO]piperidin-1-yl, 4-[(3-OHphenyl)methylNCO]piperidin-1-yl, 4-[(4-OHphenyl)methylNCO]piperidin-1-yl, 4-[(2-OHphenyl)methylNCO]piperidin-1-yl, 4-[(pyridin-2-yl)methylNCO]piperidin-1-yl, 4-[(pyridin-3-yl)methylNCO]piperidin-1-yl, 4-[(pyridin-4-yl)methylNCO]piperidin-1-yl, 4-[(pyrimidin-2-yl)methylNCO]piperidin-1-yl, 4-[(pyrimidin-4-yl)methylNCO]piperidin-1-yl, 4-[(pyrimidin-5-yl)methylNCO]piperidin-1-yl, 4-[(3-$CO_2H$phenyl)methylNCO]piperidin-1-yl, 4-[(4-$CO_2H$phenyl)methylNCO]piperidin-1-yl, 4-[(2-$CO_2H$phenyl)methylNCO]piperidin-1-yl, 4-[(3-$CH_3$phenylmethyl)NHCO]piperidin-1-yl, 4-[(4-$CH_3$phenylmethyl)NHCO]piperidin-1-yl, 4-[(2-$CH_3$phenylmethyl)NHCO]piperidin-1-yl, 4-[(3-$CONH_2$phenylmethyl)NHCO]piperidin-1-yl, 4-[(4-$CONH_2$phenylmethyl)NHCO]piperidin-1-yl, 4-[(2-$CONH_2$phenylmethyl)NHCO]piperidin-1-yl, 4-[(3-Fphenylmethyl)NHCO]piperidin-1-yl, 4-[(4-Fphenylmethyl)NHCO]piperidin-1-yl, 4-[(2-Fphenylmethyl)NHCO]piperidin-1-yl, 4-[(3-$OCH_3$phenylmethyl)NHCO]piperidin-1-yl, 4-[(4-$OCH_3$phenylmethyl)NHCO]piperidin-1-yl, 4-[(2-$OCH_3$phenylmethyl)NHCO]piperidin-1-yl, 4-[(3-CNphenylmethyl)NHCO]piperidin-1-yl, 4-[(4-CNphenylmethyl)NHCO]piperidin-1-yl, 4-[(2-CNphenylmethyl)NHCO]piperidin-1-yl, 4-[(3-OHphenylmethyl)NHCO]piperidin-1-yl, 4-[(4-OHphenylmethyl)NHCO]piperidin-1-yl, 4-[(2-OHphenylmethyl)NHCO]piperidin-1-yl, 4-[(pyridin-2-ylmethyl)NHCO]piperidin-1-yl, 4-[(pyridin-3-ylmethyl)NHCO]piperidin-1-yl, 4-[(pyridin-4-ylmethyl)NHCO]piperidin-1-yl, 4-[(pyrimidin-2-ylmethyl)NHCO]piperidin-1-yl, 4-[(pyrimidin-4-ylmethyl)NHCO]piperidin-1-yl, 4-[(pyrimidin-5-ylmethyl)NHCO]piperidin-1-yl, 4-[(3-$CO_2H$phenylmethyl)NHCO]piperidin-1-yl, 4-[(4-$CO_2H$phenylmethyl)NHNCO]-piperidin-1-yl, 4-[(2-$CO_2H$phenylmethyl)NHCO]piperidin-1-yl, 4-[(pyrazin-2-ylmethyl)-NHCO]piperidin-1-yl, 4-[(pyridazin-3-ylmethyl)NHCO]piperidin-1-yl, 4-[(pyridazin-4-ylmethyl)NHCO]piperidin-1-yl, 4-[([1.3.5]triazin-2-ylmethyl)NHCO]piperidin-1-yl, 4-[*N*-(3-$CH_3$phenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(4-$CH_3$phenylmethyl)N($CH_3$)CO]piperidin-

1-yl, 4-[ *N*-(2-$CH_3$phenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(3-$CONH_2$phenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(4-$CONH_2$phenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(2-$CONH_2$phenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(3-Fphenylmethyl)N($CH_3$)CO]-piperidin-1-yl, 4-[ *N*-(4-Fphenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(2-Fphenylmethyl)-N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(3-$OCH_3$phenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(4-$OCH_3$phenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(2-$OCH_3$phenylmethyl)N($CH_3$)CO]-piperidin-1-yl, 4-[ *N*-(3-CNphenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(4-CNphenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(2-CNphenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(3-OHphenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(4-OHphenylmethyl)N($CH_3$)CO]-piperidin-1-yl, 4-[ *N*-(2-OHphenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyridin-2-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyridin-3-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyridin-4-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyrimidin-2-ylmethyl)N($CH_3$)CO]-piperidin-1-yl, 4-[ *N*-(pyrimidin-4-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyrimidin-5-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(3-$CO_2$Hphenylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(4-$CO_2$Hphenylmethyl)N($CH_3$)NCO]piperidin-1-yl, 4-[ *N*-(2-$CO_2$Hphenylmethyl)-N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyrazin-2-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyridazin-3-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-[ *N*-(pyridazin-4-ylmethyl)N($CH_3$)CO]-piperidin-1-yl, 4-[ *N*-([1.3.5]triazin-2-ylmethyl)N($CH_3$)CO]piperidin-1-yl, 4-(pyridin-4-yl)piperidin-1-yl, 4-(pyridin-3-yl)piperidin-1-yl, 4-(pyridin-2-yl)piperidin-1-yl, 4-(pyrimidin-4-yl)piperidin-1-yl, 4-(pyrimidin-2-yl)piperidin-1-yl, 4-(pyrimidin-5-yl)piperidin-1-yl, 4-([1.3.5]triazin-2-yl)piperidin-1-yl, 4-(phenyl)piperidin-1-yl, 4-(pyrazin-2-yl)piperidin-1-yl, 4-(pyridazin-3-yl)piperidin-1-yl, 4-(pyridazin-4-yl)piperidin-1-yl, 4-(4-Fphenyl)piperidin-1-yl, 4-(3-Fphenyl)piperidin-1-yl, 4-(2-Fphenyl)piperidin-1-yl, 4-(2,4-diFphenyl)piperidin-1-yl, 4-(2,3-diFphenyl)piperidin-1-yl, 4-(2,5-diFphenyl)piperidin-1-yl, 4-(2,6-diFphenyl)piperidin-1-yl, 4-(2,4,6-triFphenyl)piperidin-1-yl, 4-(2,3,6-triFphenyl)piperidin-1-yl, 4-(2,3,4-triFphenyl)-piperidin-1-yl, 4-(4-$CH_3$Ophenyl)piperidin-1-yl, 4-(3-$CH_3$Ophenyl)piperidin-1-yl, 4-(2-$CH_3$Ophenyl)piperidin-1-yl, 4-(4-CNphenyl)piperidin-1-yl, 4-(3-CNphenyl)piperidin-1-yl, 4-(2-CNphenyl)piperidin-1-yl, 4-(4-$CO_2$Hphenyl)piperidin-1-yl, 4-(3-$CO_2$Hphenyl)piperidin-1-yl, 4-(2-$CO_2$Hphenyl)piperidin-1-yl, 4-(4-$CONH_2$phenyl)piperidin-1-yl, 4-(3-$CONH_2$phenyl)-piperidin-1-yl, 4-(2-$CONH_2$phenyl)piperidin-1-yl, 4-(methylcarbonyl)piperidin-1-yl, 4-(trifluoromethylcarbonyl)piperidin-1-yl, 4-(ethylcarbonyl)piperidin-1-yl, 4-(isopropylcarbonyl)-piperidin-1-yl, 4-(*tert*-butylcarbonyl)piperidin-1-yl, 4-(cyclopropylCO)piperidin-1-yl, 4-(cyclobutylCO)piperidin-1-yl, 4-(cyclopentylCO)piperidin-1-yl, 4-(azetidin-3-ylCO)piperidin-1-yl, 4-(3-$CH_3$Opyrrolidin-1-ylCO)piperidin-1-yl, 4-(3-$CF_3$Opyrrolidin-1-ylCO)piperidin-1-yl,

4-(3-$CHF_2O$pyrrolidin-1-ylCO)piperidin-1-yl, 4-(3-$CO_2H$pyrrolidin-1-ylCO)piperidin-1-yl, 4-(3-CNpyrrolidin-1-ylCO)piperidin-1-yl, 4-(3-$CONH_2$pyrrolidin-1-ylCO)piperidin-1-yl, 4-(pyrrolidin-1-ylCO)piperidin-1-yl, 4(oxazolidin-3-ylCO)piperidin-1-yl, 4-(tetrahydrofuran-3-ylCO)piperidin-1-yl, 4-(tetrahydrothiophen-3-ylCO)piperidin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-tetrahydrothiophen-3-ylCO)piperidin-1-yl, 4-(cyclohexylCO)piperidin-1-yl, 4-(tetrahydropyran-4-ylCO)piperidin-1-yl, 4-(piperidin-4-ylCO)piperidin-1-yl, 4-(tetrahydrothiopyran-4-ylCO)piperidin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-4-ylCO)piperidin-1-yl, 4-(piperidin-1-ylCO)piperidin-1-yl, 4-(morpholin-4-ylCO)piperidin-1-yl, 4-(thiomorpholin-4-ylCO)piperidin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-ylCO)piperidin-1-yl, 4-(piperazin-1-ylCO)piperidin-1-yl, 4-(phenylCO)piperidin-1-yl, 4-(2-$CH_3$phenylCO)piperidin-1-yl, 4-(3-$CH_3$phenylCO)piperidin-1-yl, 4-(4-$CH_3$phenylCO)piperidin-1-yl, 4-(2-FphenylCO)piperidin-1-yl, 4-(3-FphenylCO)piperidin-1-yl, 4-(4-FphenylCO)piperidin-1-yl, 4-(2-OHphenylCO)-piperidin-1-yl, 4-(3-OHphenylCO)piperidin-1-yl, 4-(4-OHphenylCO)piperidin-1-yl, 4-(2-$CH_3O$phenylCO)piperidin-1-yl, 4-(3-$CH_3O$phenylCO)piperidin-1-yl, 4-(4-$CH_3O$phenylCO)-piperidin-1-yl, 4-(2-$CO_2H$phenylCO)piperidin-1-yl, 4-(3-$CO_2H$phenylCO)piperidin-1-yl, 4-(4-$CO_2H$phenylCO)piperidin-1-yl, 4-(2-$CONH_2$phenylCO)piperidin-1-yl, 4-(3-$CONH_2$phenylCO)-piperidin-1-yl, 4-(4-$CONH_2$phenylCO)piperidin-1-yl, 4-(2-CNphenylCO)piperidin-1-yl, 4-(3-CNphenylCO)piperidin-1-yl, 4-(4-CNphenylCO)piperidin-1-yl, 4-(pyridin-4-ylCO)piperidin-1-yl, 4-(pyridin-3-ylCO)piperidin-1-yl, 4-(pyridin-2-ylCO)piperidin-1-yl, 4-(pyrimidin-4-ylCO)piperidin-1-yl, 4-(pyrimidin-2-ylCO)piperidin-1-yl, 4-(pyrimidin-5-ylCO)piperidin-1-yl 4-(benzylCO)piperidin-1-yl, 4-(2-FphenylmethylCO)piperidin-1-yl, 4-(3-FphenylmethylCO)-piperidin-1-yl, 4-(4-FphenylmethylCO)piperidin-1-yl, 4-(2-OHphenylmethylCO)piperidin-1-yl, 4-(3-OHphenylmethylCO)piperidin-1-yl, 4-(4-OHphenylmethylCO)piperidin-1-yl, 4-(2-$CH_3O$phenylmethylCO)piperidin-1-yl, 4-(3-$CH_3O$phenylmethylCO)piperidin-1-yl, 4-(4-$CH_3O$phenylmethylCO)piperidin-1-yl, 4-(2-$CO_2H$phenylmethylCO)piperidin-1-yl, 4-(3-$CO_2H$phenylmethylCO)piperidin-1-yl, 4-(4-$CO_2H$phenylmethylCO)piperidin-1-yl, 4-(2-$CONH_2$phenylmethylCO)piperidin-1-yl, 4-(3-$CONH_2$phenylmethylCO)piperidin-1-yl, 4-(4-$CONH_2$phenylmethylCO)piperidin-1-yl, 4-(2-CNphenylmethylCO)piperidin-1-yl, 4-(3-CNphenylmethylCO)piperidin-1-yl, 4-(4-CNphenylmethylCO)piperidin-1-yl, 4-(pyridin-4-ylmethylCO)piperidin-1-yl, 4-(pyridin-3-ylmethylCO)piperidin-1-yl, 4-(pyridin-2-ylmethylCO)piperidin-1-yl, 4-(pyrimidin-4-ylmethylCO)piperidin-1-yl, 4-(pyrimidin-2-ylmethylCO)piperidin-1-yl, 4-(pyrimidin-5-ylmethylCO)piperidin-1-yl, 4-(pyriazin-2-ylmethylCO)piperidin-1-yl, 4-(phenylNHCO)piperidin-1-yl, 4-(2-FphenylNHCO)piperidin-1-yl, 4-(3-FphenylNHCO)piperidin-1-yl, 4-(4-FphenylNHCO)piperidin-1-yl, 4-(2-OHphenylNHCO)-

piperidin-1-yl, 4-(3-OHphenylNHCO)piperidin-1-yl, 4-(4-OHphenylNHCO)piperidin-1-yl, 4-(2-$CH_3$OphenylNHCO)piperidin-1-yl, 4-(3-$CH_3$OphenylNHCO)piperidin-1-yl, 4-(4-$CH_3$OphenylNHCO)piperidin-1-yl, 4-(2-$CO_2$HphenylNHCO)piperidin-1-yl, 4-(3-$CO_2$HphenylNHCO)piperidin-1-yl, 4-(4-$CO_2$HphenylNHCO)piperidin-1-yl, 4-(2-$CONH_2$phenylNHCO)-piperidin-1-yl, 4-(3-$CONH_2$phenylNHCO)piperidin-1-yl, 4-(4-$CONH_2$phenylNHCO)piperidin-1-yl, 4-(2-CNphenylNHCO)piperidin-1-yl, 4-(3-CNphenylNHCO)piperidin-1-yl, 4-(4-CNphenylNHCO)piperidin-1-yl, 4-(pyridin-4-ylNHCO)piperidin-1-yl, 4-(pyridin-3-ylNHCO)-piperidin-1-yl, 4-(pyridin-2-ylNHCO)piperidin-1-yl, 4-(pyrimidin-4-ylNHCO)piperidin-1-yl, 4-(pyrimidin-2-ylNHCO)piperidin-1-yl, 4-(pyrimidin-5-ylNHCO)piperidin-1-yl, 4-([1.3.5]triazin-2-ylNHCO)piperidin-1-yl, 4-(1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(7-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(6-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO) piperidin-1-yl, 4-(8-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO) piperidin-1-yl, 4-(7-F-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(6-F-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(8-F-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(7-$CH_3$O-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(6-$CH_3$O-1,2,3,4-tetrahydroquinolin-1-ylCO) piperidin-1-yl, 4-(8-$CH_3$O-1,2,3,4-tetrahydroquinolin-1-ylCO) piperidin-1-yl, 4-(7-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(6-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(8-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)-piperidin-1-yl, 4-(7-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(6-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(8-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(7-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(6-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(8-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)piperidin-1-yl, 4-(1,2,3,4-tetrahydro-[1,8]naphthyridin-1-ylCO)piperidin-1-yl, 4-(1,2,3,4-tetrahydro-[1,7]naphthyridin-1-ylCO)piperidin-1-yl, 4-(1,2,3,4-tetrahydro-[1,6]naphthyridin-1-ylCO)piperidin-1-yl, 4-(5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-5-ylCO)piperidin-1-yl, 4-(5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-8-ylCO)piperidin-1-yl, 4-(5,6,7,8-tetrahydropyrido[3,2-d]pyrimidin-5-ylCO)piperidin-1-yl, 4-(5,6,7,8-tetrahydropyrido[2,3-d]pyridazin-1-ylCO)piperidin-1-yl, 4-(2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(7-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(6-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(5-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(7-F-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(6-F-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl 4-(5-F-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4*N*-(7-$CH_3$O-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(6-$CH_3$O-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(5-$CH_3$O-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(7-CN-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl,

4-(6-CN-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(5-CN-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(7-OH-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(6-OH-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(5-OH-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(7-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(6-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(5-$CO_2H$-2,3-dihydro-1*H*-indol-1-ylCO)piperidin-1-yl, 4-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylCO)piperidin-1-yl, 4-(2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-1-ylCO)piperidin-1-yl, 4-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-ylCO)piperidin-1-yl, 4-(6,7-dihydro-5H-pyrrolo[2,3-b]pyrazin-5-ylCO)piperidin-1-yl, 4-(6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-7-ylCO)piperidin-1-yl, 4-(6,7-dihydro-5H-pyrrolo[3,2-d]pyrimidin-5-ylCO)piperidin-1-yl, or 4-(2,3-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-ylCO)piperidin-1-yl.

(i) Within the above preferred group A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 and the preferred groups contained therein, a more preferred group of compounds is that wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form piperazin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 4-(2,2,2-trifluoroethyl)piperazin-1-yl, 4-(2-isopropyl)piperazin-1-yl, 4-(2-trifluoromethyl-2,2,2-trifluoroethyl)piperazin-1-yl 4-(cyclopropyl)piperazin-1-yl, 4-(cyclobutyl)piperazin-1-yl, 4-(oxetan-3-yl)piperazin-1-yl 4-(azetidin-3-yl)piperazin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-thietan-3-yl)piperazin-1-yl, 4-(cyclopentyl)-piperazin-1-yl, 4-(3-$CH_3O$cyclopentyl)piperazin-1-yl, 4-(3-$CHF_2O$cyclopentyl)piperazin-1-yl, 4-(3-$CF_3O$cyclopentyl)piperazin-1-yl, 4-(3-phenoxycyclopentyl)piperazin-1-yl, 4-[3-(4-Fphenoxy)cyclopentyl]piperazin-1-yl, 4-[3-(4-Clphenoxy)cyclopentyl]piperazin-1-yl, 4-[3-(4-Brphenoxy)cyclopentyl]piperazin-1-yl, 4-[3-(4-$CO_2H$phenoxy)cyclopentyl]piperazin-1-yl, 4-[3-(4-CNphenoxy)cyclopentyl]piperazin-1-yl, 4-[3-(4-$CONH_2$phenoxy)cyclopentyl]piperazin-1-yl, 4-(cyclohexyl)piperazin-1-yl, 4-(tetrahydropyran-4-yl)piperazin-1-yl, 4-(piperidin-4-yl)piperazin-1-yl, 4-(tetrahydropyran-3-yl)piperazin-1-yl, 4-(tetrahydrothiopyran-3-yl)piperazin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-3-yl)piperazin-1-yl, 4-(piperidin-3-yl)piperazin-1-yl, 4-(methylsulfonyl)piperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 4-(isopropylsulfonyl)-piperazin-1-yl, 4-(*tert*-butylsulfonyl)piperazin-1-yl, 4-(cyclopropylsulfonyl)piperazin-1-yl, 4-(cyclobutyl-sulfonyl)piperazin-1-yl, 4-(cyclopentylsulfonyl)piperazin-1-yl, 4-(cyclohexyl-sulfonyl)piperazin-1-yl, 4-(benzenesulfonyl)piperazin-1-yl, 4-(2-$CH_3$phenylsulfonyl)piperazin-1-yl, 4-(3-$CH_3$phenylsulfonyl)piperazin-1-yl, 4-(4-$CH_3$phenylsulfonyl)piperazin-1-yl, 4-(2-Fphenyl-sulfonyl)piperazin-1-yl, 4-(3-Fphenylsulfonyl)piperazin-1-yl, 4-(4-Fphenyl-sulfonyl)piperazin-1-yl, 4-(2-OHphenylsulfonyl)piperazin-1-yl, 4-(3-OHphenylsulfonyl)-piperazin-1-yl, 4-(4-OHphenylsulfonyl)piperazin-1-yl, 4-(2-$CH_3O$phenylsulfonyl)piperazin-1-yl,

4-(3-$CH_3O$phenylsulfonyl)piperazin-1-yl, 4-(4-$CH_3O$phenylsulfonyl)piperazin-1-yl, 4-(2-$CO_2H$-phenylsulfonyl)piperazin-1-yl, 4-(3-$CO_2H$phenylsulfonyl)piperazin-1-yl, 4-(4-$CO_2H$phenyl-sulfonyl)piperazin-1-yl, 4-(2-$CONH_2$phenylsulfonyl)piperazin-1-yl, 4-(3-$CONH_2$phenyl-sulfonyl)piperazin-1-yl, 4-(4-$CONH_2$phenylsulfonyl)piperazin-1-yl, 4-(2-$CON(CH_3)_2$phenyl-sulfonyl)piperazin-1-yl, 4-(3-$CON(CH_3)_2$phenylsulfonyl)piperazin-1-yl, 4-(4-$CON(CH_3)_2$phenylsulfonyl)piperazin-1-yl, 4-(methylphenylNCO)piperazin-1-yl, 4-[(3-$CONH_2$phenyl)methylNCO]piperazin-1-yl, 4-[(4-$CONH_2$phenyl)methylNCO]piperazin-1-yl, 4-[(2-$CONH_2$phenyl)methylNCO]piperazin-1-yl, 4-[(3-Fphenyl)methylNCO]piperazin-1-yl, 4-[(4-Fphenyl)methylNCO]piperazin-1-yl, 4-[(2-Fphenyl)methylNCO]piperazin-1-yl, 4-[(3-$OCH_3$phenyl)methylNCO]piperazin-1-yl, 4-[(4-$OCH_3$phenyl)methylNCO]piperazin-1-yl, 4-[(2-$OCH_3$phenyl)methylNCO]piperazin-1-yl, 4-[(3-CNphenyl)methylNCO]piperazin-1-yl, 4-[(4-CNphenyl)methylNCO]piperazin-1-yl, 4-[(2-CNphenyl)methylNCO]piperazin-1-yl, 4-[(3-OHphenyl)methylNCO]piperazin-1-yl, 4-[(4-OHphenyl)methylNCO]piperazin-1-yl, 4-[(2-OHphenyl)methylNCO]piperazin-1-yl, 4-[(pyridin-2-yl)methylNCO]piperazin-1-yl, 4-[(pyridin-3-yl)methylNCO]piperazin-1-yl, 4-[(pyridin-4-yl)methylNCO]piperazin-1-yl, 4-[(pyrimidin-2-yl)methylNCO]piperazin-1-yl, 4-[(pyrimidin-4-yl)methylNCO]piperazin-1-yl, 4-[(pyrimidin-5-yl)methylNCO]piperazin-1-yl, 4-[(3-$CO_2H$phenyl)methylNCO]piperazin-1-yl, 4-[(4-$CO_2H$phenyl)methylNCO]piperazin-1-yl, 4-[(2-$CO_2H$phenyl)methylNCO]piperazin-1-yl, 4-[(3-$CH_3$phenylmethyl)NHCO]piperazin-1-yl, 4-[(4-$CH_3$phenylmethyl)NHCO]piperazin-1-yl, 4-[(2-$CH_3$phenylmethyl)NHCO]piperazin-1-yl, 4-[(3-$CONH_2$phenylmethyl)NHCO]piperazin-1-yl, 4-[(4-$CONH_2$phenylmethyl)NHCO]piperazin-1-yl, 4-[(2-$CONH_2$phenylmethyl)NHCO]piperazin-1-yl, 4-[(3-Fphenylmethyl)NHCO]piperazin-1-yl, 4-[(4-Fphenylmethyl)NHCO]piperazin-1-yl, 4-[(2-Fphenylmethyl)NHCO]piperazin-1-yl, 4-[(3-$OCH_3$phenylmethyl)NHCO]piperazin-1-yl, 4-[(4-$OCH_3$phenylmethyl)NHCO]piperazin-1-yl, 4-[(2-$OCH_3$phenylmethyl)NHCO]piperazin-1-yl, 4-[(3-CNphenylmethyl)NHCO]piperazin-1-yl, 4-[(4-CNphenylmethyl)NHCO]piperazin-1-yl, 4-[(2-CNphenylmethyl)NHCO]piperazin-1-yl, 4-[(3-OHphenylmethyl)NHCO]piperazin-1-yl, 4-[(4-OHphenylmethyl)NHCO]piperazin-1-yl, 4-[(2-OHphenylmethyl)NHCO]piperazin-1-yl, 4-[(pyridin-2-ylmethyl)NHCO]piperazin-1-yl, 4-[(pyridin-3-ylmethyl)NHCO]piperazin-1-yl, 4-[(pyridin-4-ylmethyl)NHCO]piperazin-1-yl, 4-[(pyrimidin-2-ylmethyl)NHCO]piperazin-1-yl, 4-[(pyrimidin-4-ylmethyl)NHCO]piperazin-1-yl, 4-[(pyrimidin-5-ylmethyl)NHCO]piperazin-1-yl, 4-[(3-$CO_2H$phenylmethyl)NHCO]piperazin-1-yl, 4-[(4-$CO_2H$phenylmethyl)NHNCO]-piperazin-1-yl, 4-[(2-$CO_2H$phenylmethyl)NHCO]piperazin-1-yl, 4-[(pyrazin-2-ylmethyl)-NHCO]piperazin-1-yl, 4-[(pyridazin-3-ylmethyl)NHCO]piperazin-1-yl, 4-[(pyridazin-4-ylmethyl)NHCO]piperazin-1-yl, 4-[([1.3.5]triazin-2-ylmethyl)NHCO]piperazin-1-yl, 4-[*N*-(3-

$CH_3$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(4-$CH_3$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(2-$CH_3$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(3-$CONH_2$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(4-$CONH_2$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(2-$CONH_2$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(3-Fphenylmethyl)N($CH_3$)CO]-piperazin-1-yl, 4-[ *N*-(4-Fphenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(2-Fphenylmethyl)-N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(3-$OCH_3$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(4-$OCH_3$phenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(2-$OCH_3$phenylmethyl)N($CH_3$)CO]-piperazin-1-yl, 4-[ *N*-(3-CNphenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(4-CNphenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(2-CNphenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(3-OHphenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(4-OHphenylmethyl)N($CH_3$)CO]-piperazin-1-yl, 4-[ *N*-(2-OHphenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyridin-2-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyridin-3-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyridin-4-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyrimidin-2-ylmethyl)N($CH_3$)CO]-piperazin-1-yl, 4-[ *N*-(pyrimidin-4-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyrimidin-5-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(3-$CO_2$Hphenylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(4-$CO_2$Hphenylmethyl)N($CH_3$)NCO]piperazin-1-yl, 4-[ *N*-(2-$CO_2$Hphenylmethyl)-N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyrazin-2-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyridazin-3-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-[ *N*-(pyridazin-4-ylmethyl)N($CH_3$)CO]-piperazin-1-yl, 4-[ *N*-([1.3.5]triazin-2-ylmethyl)N($CH_3$)CO]piperazin-1-yl, 4-(pyridin-4-yl)piperazin-1-yl, 4-(pyridin-3-yl)piperazin-1-yl, 4-(pyridin-2-yl)piperazin-1-yl, 4-(pyrimidin-4-yl)piperazin-1-yl, 4-(pyrimidin-2-yl)piperazin-1-yl, 4-(pyrimidin-5-yl)piperazin-1-yl, 4-([1.3.5]triazin-2-yl)piperazin-1-yl, 4-(phenyl)piperazin-1-yl, 4-(pyrazin-2-yl)piperazin-1-yl, 4-(pyridazin-3-yl)piperazin-1-yl, 4-(pyridazin-4-yl)piperazin-1-yl, 4-(4-Fphenyl)piperazin-1-yl, 4-(3-Fphenyl)piperazin-1-yl, 4-(2-Fphenyl)piperazin-1-yl, 4-(2,4-diFphenyl)piperazin-1-yl, 4-(2,3-diFphenyl)piperazin-1-yl, 4-(2,5-diFphenyl)piperazin-1-yl, 4-(2,6-diFphenyl)piperazin-1-yl, 4-(2,4,6-triFphenyl)piperazin-1-yl, 4-(2,3,6-triFphenyl)piperazin-1-yl, 4-(2,3,4-triFphenyl)-piperazin-1-yl, 4-(4-$CH_3$Ophenyl)piperazin-1-yl, 4-(3-$CH_3$Ophenyl)piperazin-1-yl, 4-(2-$CH_3$Ophenyl)piperazin-1-yl, 4-(4-CNphenyl)piperazin-1-yl, 4-(3-CNphenyl)piperazin-1-yl, 4-(2-CNphenyl)piperazin-1-yl, 4-(4-$CO_2$Hphenyl)piperazin-1-yl, 4-(3-$CO_2$Hphenyl)piperazin-1-yl, 4-(2-$CO_2$Hphenyl)piperazin-1-yl, 4-(4-$CONH_2$phenyl)piperazin-1-yl, 4-(3-$CONH_2$phenyl)-piperazin-1-yl, 4-(2-$CONH_2$phenyl)piperazin-1-yl, 4-(methylcarbonyl)piperazin-1-yl, 4-(trifluoromethylcarbonyl)piperazin-1-yl, 4-(ethylcarbonyl)piperazin-1-yl, 4-(isopropylcarbonyl)-piperazin-1-yl, 4-(*tert*-butylcarbonyl)piperazin-1-yl, 4-(cyclopropylCO)piperazin-1-yl, 4-(cyclobutylCO)piperazin-1-yl, 4-(cyclopentylCO)piperazin-1-yl, 4-(azetidin-3-ylCO)piperazin-

1-yl, 4-(3-$CH_3$Opyrrolidin-1-ylCO)piperazin-1-yl, 4-(3-$CF_3$Opyrrolidin-1-ylCO)piperazin-1-yl, 4-(3-$CHF_2$Opyrrolidin-1-ylCO)piperazin-1-yl, 4-(3-$CO_2$Hpyrrolidin-1-ylCO)piperazin-1-yl, 4-(3-CNpyrrolidin-1-ylCO)piperazin-1-yl, 4-(3-$CONH_2$pyrrolidin-1-ylCO)piperazin-1-yl, 4-(pyrrolidin-1-ylCO)piperazin-1-yl, 4(oxazolidin-3-ylCO)piperazin-1-yl, 4-(tetrahydrofuran-3-ylCO)piperazin-1-yl, 4-(tetrahydrothiophen-3-ylCO)piperazin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-tetrahydrothiophen-3-ylCO)piperazin-1-yl, 4-(cyclohexylCO)piperazin-1-yl, 4-(tetrahydropyran-4-ylCO)piperazin-1-yl, 4-(piperdin-1-ylCO)piperazin-1-yl, 4-(tetrahydrothiopyran-4-ylCO)piperazin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-hexahydrothiopyran-4-ylCO)piperazin-1-yl, 4-(piperidin-1-ylCO)piperazin-1-yl, 4-(morpholin-4-ylCO)piperazin-1-yl, 4-(thiomorpholin-4-ylCO)piperazin-1-yl, 4-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-ylCO)piperazin-1-yl, 4-(piperazin-1-ylCO)piperazin-1-yl, 4-(phenylCO)piperazin-1-yl, 4-(2-$CH_3$phenylCO)piperazin-1-yl, 4-(3-$CH_3$phenylCO)piperazin-1-yl, 4-(4-$CH_3$phenylCO)piperazin-1-yl, 4-(2-FphenylCO)piperazin-1-yl, 4-(3-FphenylCO)piperazin-1-yl, 4-(4-FphenylCO)piperazin-1-yl, 4-(2-OHphenylCO)-piperazin-1-yl, 4-(3-OHphenylCO)piperazin-1-yl, 4-(4-OHphenylCO)piperazin-1-yl, 4-(2-$CH_3$OphenylCO)piperazin-1-yl, 4-(3-$CH_3$OphenylCO)piperazin-1-yl, 4-(4-$CH_3$OphenylCO)-piperazin-1-yl, 4-(2-$CO_2$HphenylCO)piperazin-1-yl, 4-(3-$CO_2$HphenylCO)piperazin-1-yl, 4-(4-$CO_2$HphenylCO)piperazin-1-yl, 4-(2-$CONH_2$phenylCO)piperazin-1-yl, 4-(3-$CONH_2$phenylCO)-piperazin-1-yl, 4-(4-$CONH_2$phenylCO)piperazin-1-yl, 4-(2-CNphenylCO)piperazin-1-yl, 4-(3-CNphenylCO)piperazin-1-yl, 4-(4-CNphenylCO)piperazin-1-yl, 4-(pyridin-4-ylCO)piperazin-1-yl, 4-(pyridin-3-ylCO)piperazin-1-yl, 4-(pyridin-2-ylCO)piperazin-1-yl, 4-(pyrimidin-4-ylCO)piperazin-1-yl, 4-(pyrimidin-2-ylCO)piperazin-1-yl, 4-(pyrimidin-5-ylCO)piperazin-1-yl 4-(benzylCO)piperazin-1-yl, 4-(2-FphenylmethylCO)piperazin-1-yl, 4-(3-FphenylmethylCO)-piperazin-1-yl, 4-(4-FphenylmethylCO)piperazin-1-yl, 4-(2-OHphenylmethylCO)piperazin-1-yl, 4-(3-OHphenylmethylCO)piperazin-1-yl, 4-(4-OHphenylmethylCO)piperazin-1-yl, 4-(2-$CH_3$OphenylmethylCO)piperazin-1-yl, 4-(3-$CH_3$OphenylmethylCO)piperazin-1-yl, 4-(4-$CH_3$OphenylmethylCO)piperazin-1-yl, 4-(2-$CO_2$HphenylmethylCO)piperazin-1-yl, 4-(3-$CO_2$HphenylmethylCO)piperazin-1-yl, 4-(4-$CO_2$HphenylmethylCO)piperazin-1-yl, 4-(2-$CONH_2$phenylmethylCO)piperazin-1-yl, 4-(3-$CONH_2$phenylmethylCO)piperazin-1-yl, 4-(4-$CONH_2$phenylmethylCO)piperazin-1-yl, 4-(2-CNphenylmethylCO)piperazin-1-yl, 4-(3-CNphenylmethylCO)piperazin-1-yl, 4-(4-CNphenylmethylCO)piperazin-1-yl, 4-(pyridin-4-ylmethylCO)piperazin-1-yl, 4-(pyridin-3-ylmethylCO)piperazin-1-yl, 4-(pyridin-2-ylmethylCO)piperazin-1-yl, 4-(pyrimidin-4-ylmethylCO)piperazin-1-yl, 4-(pyrimidin-2-ylmethylCO)piperazin-1-yl, 4-(pyrimidin-5-ylmethylCO)piperazin-1-yl, 4-(pyriazin-2-ylmethylCO)piperazin-1-yl, 4-(phenylNHCO)piperazin-1-yl, 4-(2-FphenylNHCO)piperazin-1-

yl, 4-(3-FphenylNHCO)piperazin-1-yl, 4-(4-FphenylNHCO)piperazin-1-yl, 4-(2-OHphenyl-NHCO)-piperazin-1-yl, 4-(3-OHphenylNHCO)piperazin-1-yl, 4-(4-OHphenylNHCO)piperazin-1-yl, 4-(2-$CH_3$OphenylNHCO)piperazin-1-yl, 4-(3-$CH_3$OphenylNHCO)piperazin-1-yl, 4-(4-$CH_3$OphenylNHCO)piperazin-1-yl, 4-(2-$CO_2$HphenylNHCO)piperazin-1-yl, 4-(3-$CO_2$Hphenyl-NHCO)piperazin-1-yl, 4-(4-$CO_2$HphenylNHCO)piperazin-1-yl, 4-(2-$CONH_2$phenylNHCO)-piperazin-1-yl, 4-(3-$CONH_2$phenylNHCO)piperazin-1-yl, 4-(4-$CONH_2$phenylNHCO)piperazin-1-yl, 4-(2-CNphenylNHCO)piperazin-1-yl, 4-(3-CNphenylNHCO)piperazin-1-yl, 4-(4-CNphenylNHCO)piperazin-1-yl, 4-(pyridin-4-ylNHCO)piperazin-1-yl, 4-(pyridin-3-ylNHCO)-piperazin-1-yl, 4-(pyridin-2-ylNHCO)piperazin-1-yl, 4-(pyrimidin-4-ylNHCO)piperazin-1-yl, 4-(pyrimidin-2-ylNHCO)piperazin-1-yl, 4-(pyrimidin-5-ylNHCO)piperazin-1-yl, 4-([1.3.5]triazin-2-ylNHCO)piperazin-1-yl, 4-(1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(7-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(6-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO) piperazin-1-yl, 4-(8-$CONH_2$-1,2,3,4-tetrahydroquinolin-1-ylCO) piperazin-1-yl, 4-(7-F-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(6-F-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(8-F-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(7-$CH_3$O-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(6-$CH_3$O-1,2,3,4-tetrahydroquinolin-1-ylCO) piperazin-1-yl, 4-(8-$CH_3$O-1,2,3,4-tetrahydroquinolin-1-ylCO) piperazin-1-yl, 4-(7-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(6-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(8-CN-1,2,3,4-tetrahydroquinolin-1-ylCO)-piperazin-1-yl, 4-(7-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(6-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(8-OH-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(7-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(6-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(8-$CO_2$H-1,2,3,4-tetrahydroquinolin-1-ylCO)piperazin-1-yl, 4-(1,2,3,4-tetrahydro-[1,8]naphthyridin-1-ylCO)piperazin-1-yl, 4-(1,2,3,4-tetrahydro-[1,7]naphthyridin-1-ylCO)piperazin-1-yl, 4-(1,2,3,4-tetrahydro-[1,6]naphthyridin-1-ylCO)piperazin-1-yl, 4-(5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-5-ylCO)piperazin-1-yl, 4-(5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-8-ylCO)piperazin-1-yl, 4-(5,6,7,8-tetrahydropyrido[3,2-d]pyrimidin-5-ylCO)piperazin-1-yl, 4-(5,6,7,8-tetrahydropyrido[2,3-d]pyridazin-1-ylCO)piperazin-1-yl, 4-(2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(7-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(6-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(5-$CONH_2$-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(7-F-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(6-F-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(5-F-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4*N*-(7-$CH_3$O-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(6-$CH_3$O-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(5-$CH_3$O-2,3-

dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(7-CN-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(6-CN-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(5-CN-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(7-OH-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(6-OH-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(5-OH-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(7-$CO_2$H-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(6-$CO_2$H-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(5-$CO_2$H-2,3-dihydro-1*H*-indol-1-ylCO)piperazin-1-yl, 4-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylCO)piperazin-1-yl, 4-(2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-1-ylCO)piperazin-1-yl, 4-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-ylCO)piperazin-1-yl, 4-(6,7-dihydro-5H-pyrrolo[2,3-b]pyrazin-5-ylCO)piperazin-1-yl, 4-(6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-7-ylCO)piperazin-1-yl, 4-(6,7-dihydro-5H-pyrrolo[3,2-d]pyrimidin-5-ylCO)piperazin-1-yl, or 4-(2,3-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-ylCO)piperazin-1-yl.

It should be recognized by a person skilled in the art that certain specific groups listed in (g), (h), and (i) above may not be within the scope of preferred groups A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 due to the limitation set forth in such preferred groups. Hence, whether a particular group set forth in (g), (h), and (i) is within the scope of preferred groups A, A1, A2, A3, A4, A5, A6, A7, A8, B, B1, B2, B3, B4, B5, B6, B7, B8, C, C1, C2, C3, C4, C5, C6, C7, and C8 should be determined in light of the limitation(s) present in each individual preferred group.

Within the above preferred groups A, A(a-f), A1, A1(a-i), A2, A2(a-i), A3, A3(a-i), A4, A4(a-i), A5, A5(a-i), A6(a-i), A7(a-i), A8(a-i), B, B(a-i), B1, B1(a-i), B2, B2(a-i), B3, B3(a-i), B4, B4(a-i), B5, B5(a-i), B6(a-i), B7(a-i), B8(a-i), C, C(a-f), C1, C1(a-i), C2, C2(a-i), C3, C3(a-i), C4, C4(a-i), C5, C5(a-i), C6(a-i), C7(a-i), and C8(a-i), and the more preferred groups contained therein, a particularly preferred group of compounds is that wherein:

$R^{4a}$ is $-CHF_2$, $-CF_3$, or $-CF_2CF_3$; preferably $-CF_3$; and

the stereochemistry at the carbon to which $R^3$ is attached is (*R*) and to which $R^4$ is attached is (*S*).

Within the above preferred groups A, A(a-i), A1, A1(a-i), A2, A2(a-i), A3, A3(a-i), A4, A4(a-i), A5, A5(a-i), A6(a-i), A7(a-i), A8(a-i), B, B(a-i), B1, B1(a-i), B2, B2(a-i), B3, B3(a-i), B4, B4(a-i), B5, B5(a-i), B6(a-i), B7(a-i), B8(a-i), C, C(a-i), C1, C1(a-i), C2, C2(a-i), C3, C3(a-i), C4, C4(a-i), C5, C5(a-i), C6(a-i), C7(a-i), and C8(a-i), and the more preferred groups contained therein, a particularly preferred group of compounds is that wherein:

$R^{4a}$ is $-CHF_2$, $-CF_3$, or $-CF_2CF_3$; preferably $-CF_3$; and

the stereochemistry at the carbon to which $R^3$ is attached is (*R*) and to which $R^4$ is attached is (*S*).

II. Certain compounds of Formula (Ia) within the broadest scope set forth in the Summary of the Invention are preferred. For example:

A'. One preferred group of compounds is that wherein $R^1$ and $R^2$ are hydrogen.

B'. Another preferred group of compounds is that wherein $R^1$ and $R^2$ together with the carbon atom to which they are attached form cycloalkylene, preferably $R^1$ and $R^2$ together with the carbon atom to which they are attached form cyclopropylene.

C'. Another preferred group of compounds is that wherein $R^1$ and $R^2$ together with the carbon atom to which they are attached form tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-dioxohexahydrothiopyran-4-yl.

(a') Within the above preferred groups A, B, and C and the more preferred groups contained therein, an even more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ is hydrogen, alkyl, acyl, and $R^6$ is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ is optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl, and one $R^c$ selected from hydroxyalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or acyl wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo.

(b') Within the above preferred groups A, B, and C and the more preferred groups contained therein, another even more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ is haloalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, or heterocycloalkylalkyl and $R^6$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ is optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl, and one $R^c$ selected from hydroxyalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, or acyl wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo.

(c') Within the above preferred groups A, B, and C and the more preferred groups contained therein, another even more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl, and one $R^c$ selected from hydroxyalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, or acyl wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo. Preferably, $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form morpholin-4-yl, thiomorpholin-4-yl, pyrrolidinyl, piperidinyl, or piperazinyl optionally substituted with one, two, or three $R^a$ independently selected from methyl, trifluoromethyl, methoxy, hydroxyl, trifluoromethoxy, or fluoro; or optionally substituted with one or two $R^b$ independently selected from methyl, trifluoromethyl, methoxy, hydroxyl, fluoro, or trifluoromethoxy and one $R^c$ selected from hydroxymethyl, hydroxypropyl, hydroxyethyl, cyclopropyl, cyclopropylmethyl, acetyl, or trifluoroacetyl. More preferably, $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form morpholin-4-yl, thiomorpholin-4-yl, pyrrolidinyl, piperidinyl, 4-methylpiperazinyl, or 4-cyclopropylpiperazinyl.

(d') Within the above preferred groups A, B, and C and the more preferred groups contained therein, another even more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2$-alkylene-heteroaryl, preferably pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinolinyl, or isoquinolinyl, wherein the heteroaryl ring is optionally substituted with one, two, or three substituents independently selected from one, two, or three $R^e$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, amino, alkylamino, dialkylamino, or acyl. Preferably, $R^3$ is 4-$CF_3$-pyridin-3-ylmethanesulfonyl-methyl, pyridin-3-ylmethanesulfonylmethyl, pyridazin-3-ylmethanesulfonylmethyl, 2-$CF_3$-furan-5-ylmethanesulfonylmethyl, pyrimidin-5-ylmethanesulfonylmethyl, 2-$CH_3$-thiazol-4-ylmethanesulfonylmethyl, or pyridin-4-ylmethanesulfonylmethyl.

(e') Within the above preferred groups A, B, and C and the more preferred groups contained therein, another even more preferred group of compounds is that wherein:

$R^3$ is –alkylene-$SO_2$-$CF_2$-heteroaryl, preferably pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinolinyl, or isoquinolinyl, wherein the heteroaryl ring is optionally substituted

with one, two, or three substituents independently selected from one, two, or three $R^c$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, amino, alkylamino, dialkylamino, or acyl. Preferably, $R^3$ is 4-$CF_3$-pyridin-3-yl-$CF_2SO_2$-methyl, pyridin-3-yl-$CF_2SO_2$-methyl, pyridazin-3-yl-$CF_2SO_2$-methyl, pyrimidin-5-yl-$CF_2SO_2$-methyl, or pyridin-4-yl-$CF_2SO_2$-methyl.

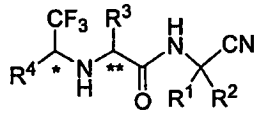
Within the above preferred groups A', A'(a'-e'), B', B'(a'-e'), C', and C'(a'-e') and the more preferred groups contained therein, a particularly preferred group of compounds is that wherein:

$R^4$ is phenyl optionally substituted with one or two fluoro. Preferably, $R^4$ is 4-fluorophenyl or 3,4-difluorophenyl;

and the stereochemistry at the carbon to which $R^3$ is attached is (*R*) and to which $R^4$ is attached is (*S*).

Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise.

Compounds of Formula (I) where $R^1$, $R^2$, $R^3$, and $R^4$ are as defined in Table I below are:



(I)

Table I

| Cpd # | Stereochem at (*C,**C) | $R^1$+$R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| 1 | (*S*,*R*) | cyclopropyl | 4-$CF_3$-pyridin-3-ylmethanesulfonylmethyl | 4-Fphenyl |
| 2 | (*S*,*R*) | cyclopropyl | pyridin-3-ylmethanesulfonylmethyl | 4-F-phenyl |
| 3 | (*S*,*R*) | cyclopropyl | pyridazin-3-ylmethanesulfonylmethyl | 4-F-phenyl |
| 4 | (*S*,*R*) | cyclopropyl | 2-$CF_3$-furan-5-ylmethanesulfonylmethyl | 4-F-phenyl |
| 5 | (*S*,*R*) | cyclopropyl | pyrimidin-5-ylmethanesulfonylmethyl | 4-F-phenyl |
| 6 | (*S*,*R*) | cyclopropyl | 2-$CH_3$-thiazol-4-ylmethanesulfonylmethyl | 4-F-phenyl |
| 7 | (*S*,*R*) | cyclopropyl | pyridin-4-ylmethanesulfonylmethyl | 4-F-phenyl |
| 8 | (*S*,*R*) | cyclopropyl | morpholin-4-ylsulfonylmethyl | 4-F-phenyl |
| 9 | (*S*,*R*) | cyclopropyl | *N*-cyclopropylaminosulfonylmethyl | 4-F-phenyl |
| 10 | (*S*,*R*) | cyclopropyl | piperidin-1-ylsulfonylmethyl | 4-F-phenyl |
| 11 | (*S*,*R*) | cyclopropyl | *N*-4-fluorobenzylaminosulfonylmethyl | 4-F-phenyl |
| 12 | (*S*,*R*) | cyclopropyl | 4-phenylpiperazin-1-ylsulfonylmethyl | 4-F-phenyl |
| 13 | (*S*,*R*) | cyclopropyl | 4-(4-fluorophenyl)piperazin-1-ylsulfonylmethyl | 4-F-phenyl |
| 14 | (*S*,*R*) | cyclopropyl | 4-$NH_2$COpiperidin-1-ylsulfonylmethyl | 4-F-phenyl |
| 15 | (*S*,*R*) | cyclopropyl | *N*-cyclohexylaminosulfonylmethyl | 4-F-phenyl |
| 16 | (*S*,*R*) | cyclopropyl | *N*-(2-morpholin-4-ylethyl)aminosulfonylmethyl | 4-F-phenyl |

| Cpd # | Stereochem at (*C,**C) | $R^1$+$R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| 17 | (*S*,*R*) | cyclopropyl | *N*-phenylaminosulfonylmethyl | 4-F-phenyl |
| 18 | (*S*,*R*) | cyclopropyl | *N*-pyridin-2-ylaminosulfonylmethyl | 4-F-phenyl |
| 19 | (*S*,*R*) | cyclopropyl | 3,4-dihydro-1*H*-isoquinolin-2-ylsulfonylmethyl | 4-F-phenyl |
| 20 | (*S*,*R*) | cyclopropyl | 2,3-dihydroindol-1-ylsulfonylmethyl | 4-F-phenyl |
| 21 | (*S*,*R*) | cyclopropyl | 4-benzyloxycarbonylpiperazin-1-ylsulfonyl-methyl | 4-F-phenyl |
| 22 | (*S*,*R*) | cyclopropyl | 2(*S*)-methoxymethylpyrrolidin-1-ylsulfonyl-methyl | 4-F-phenyl |
| 23 | (*S*,*R*) | cyclopropyl | 1(*S*),4(*S*)-5-(4-fluorophenyl)2,5-diazabicyclo-[2.2.1]heptane-2-sulfonylmethyl | 4-F-phenyl |
| 24 | (*S*,*R*) | cyclopropyl | *N*-methyl-*N*-phenylaminosulfonylmethyl | 4-F-phenyl |
| 25 | (*S*,*R*) | cyclopropyl | 1-isopropylaminocarbonylpiperazin-4-ylsulfonylmethyl | 4-F-phenyl |
| 26 | (*S*,*R*) | cyclopropyl | 1-(4-fluorophenylaminocarbonyl)piperazin-4-ylsulfonylmethyl | 4-F-phenyl |
| 27 | (*S*,*R*) | cyclopropyl | 4-benzoylpiperazin-1-ylsulfonylmethyl | 4-F-phenyl |
| 28 | (*S*,*R*) | cyclopropyl | pyrrolidin-1-ylsulfonylmethyl | 4-F-phenyl |
| 29 | (*S*,*R*) | cyclopropyl | 4-trifluoromethylpiperidin-1-ylsulfonylmethyl | 4-F-phenyl |
| 30 | (*S*,*R*) | cyclopropyl | 4-acetylpiperazin-1-ylsulfonylmethyl | 4-F-phenyl |
| 31 | (*S*,*R*) | cyclopropyl | *N*-benzyl-*N*-ethylaminosulfonylmethyl | 4-F-phenyl |
| 32 | (*S*,*R*) | cyclopropyl | 4-(pyridin-4-yl-1-yl)piperidin-1-ylsulfonylmethyl | 4-F-phenyl |
| 33 | (*S*,*R*) | cyclopropyl | 4-cyclopropylpiperazin-1-ylsulfonylmethyl | 4-F-phenyl |

| Cpd # | Stereochem at (*C,**C) | $R^1+R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| 34 | (*S*,*R*) | cyclopropyl | azepan-1-ylsulfonylmethyl | 4-F-phenyl |
| 35 | (*S*,*R*) | cyclopropyl | 4-pyridin-2-ylpiperazin-1-ylsulfonylmethyl | 4-F-phenyl |
| 36 | (*S*,*R*) | cyclopropyl | 4-cyclopropylcarbonylpiperazin-1-yl | 4-F-phenyl |

* compounds 9-36 were obtained as diasteriomeric mixture with the (*S*,*R*) distereomer being in excess. The relative ratio of the two distereomer is reported in Working Example 2 below. However, the pure diasteroisomer is being claimed as shown in table above. and are named as:

*N*-(1-cyanocyclopropyl)-3-(4-trifluoromethylpyridin-3-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

*N*-(1-cyanocyclopropyl)-3-pyridin-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide; 485(M+1), 507(M+23), 483(M-1)

*N*-(1-cyanocyclopropyl)-3-pyridan-3-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

*N*-(1-cyanocyclopropyl)-3-(2-trifluoromethylfuran-5-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

*N*-(1-cyanocyclopropyl)-3-pyrimidin-5-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

*N*-(1-cyanocyclopropyl)-3-(2-methylthiazol-4-ylmethanesulfonyl)-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

*N*-(1-cyanocyclopropyl)-3-pyridin-4-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide;

*N*-(1-cyanocyclopropyl)-3-(morpholin-4-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(cyclopropylsulfamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(piperidin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(4-fluorobenzylsulfamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(4-phenylpiperazin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-[4-(4-fluorophenyl)piperazin-1-ylsulfonyl]-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(4-aminocarbonylpiperidin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionamide;

*N*-(1-cyanocyclopropyl)-3-(cyclohexylsulfamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(2-morpholin-4-ylethylsulfamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(phenylsulfamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylsulfamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(3,4-dihydro-1*H*-isoquinolin-2-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(2,3-dihydro-1*H*-indol-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(4-benzyloxycarbonylpiperazin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionamide;

*N*-(1-cyanocyclopropyl)-3-[2(*S*)-methoxymethylpyrrolidin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionamide;

*N*-(1-cyanocyclopropyl)-3-(1(*S*),4(*S*)-5-(4-fluorophenyl)2,5diazabicyclo[2.2.1]heptane-2-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

*N*-(1-cyanocyclopropyl)-3-(*N*-methyl-*N*-phenylsulfamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;

4-{2-(1-cyanocyclopropylcarbamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]ethanesulfonyl}piperazine-1-carboxylic acid isopropylamide;

4-{2-(1-cyanocyclopropylcarbamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]ethanesulfonyl}piperazine-1-carboxylic acid (4-fluorophenyl)amide;

3-(4-benzoylpiperazin-1-ylsulfonyl)-*N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;
*N*-(1-cyanocyclopropyl)-3-(pyrrolidin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;
*N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(4-trifluoromethylpiperidin-1-ylsulfonyl)propionamide;
3-(4-acetylpiperazin-1-ylsulfonyl)-*N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;
3-(*N*-benzyl-*N*-ethylsulfamoyl)-*N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;
*N*-(1-cyanocyclopropyl)-3-[4-(pyridin-4-yl)piperadin-1-ylsulfonyl]-2(R)-[2,2,2-trifluoro-1(S)-(4-fluorophenyl)ethylamino]-propionamide;
*N*-(1-cyanocyclopropyl)-3-(4-cyclopropylpiperazin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;
3-(azepan-1-ylsulfonyl)-*N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide;
*N*-(1-cyanocyclopropyl)-3-(4-pyridin-2-ylpiperazin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide
and
*N*-(1-cyanocyclopropyl)-3-(4-cyclopropylcarbonylpiperazin-1-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionamide.

## GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Array Biopharma (Boulder, CO), AstaTechy (Monmouth Junction, ND), Bachem (Torrance, Calif.), Oakwood (West Columbia, SC), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

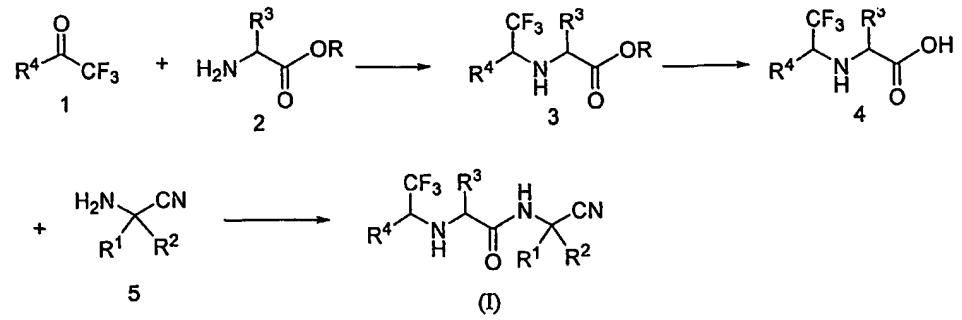
The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "*Protective Groups in Organic Chemistry*" John Wiley and Sons, 1999.

Compounds of Formulae (I) and (Ia) where $R^1$, $R^2$, $R^3$, and $R^4$ are as defined in the Summary of the Invention, $R^{4a}$ is trifluoromethyl, and $R^{4b}$ is hydrogen can be prepared by proceeding as in the following Reaction Scheme 1 below.

Scheme 1



Reaction of a ketone of formula 1 where $R^4$ is as defined in the Summary of the Invention with an α-amino ester of formula 2 where R is a carboxy protecting group, preferably an alkyl group, preferably methyl, and $R^3$ is as defined in the Summary of the Invention under reductive amination reaction conditions provide a compound of formula 3. The reaction is carried out in the presence of a suitable dehydrating agent such as $TiCl_4$ and the like, in the presence of a base such as diisopropylethylamine, pyridine, and the like and in a suitable organic solvent such as methylene chloride to give an imine. The imine is reduced with a suitable reducing agent such as sodium borohydride, sodium cyanoborohydride, and the like in a suitable organic solvent such as methanol, ethanol, and the like.

Compounds of formula 1 such as 2,2,2-trifluoromethylacetophenone is commercially available. Others can be prepared by methods well known in the art. α-Amino esters of formula 2 can be prepared by methods well known in the art. For example, a compound of formula 2 where $R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ are as defined in the Summary of the Invention can be prepared by the procedure described in Ross, D.L.; Skinner, C.G.; Shive, W. *J. Org. Chem.* **1959**, *24*, 1372-1374; b) Byrnes, S.; Burckart, G.J.; Mokotoff, M. *J. Med. Chem.* **1978**, *21*, 45-49.

Hydrolysis of the ester group in compound 3 provides a compound of formula 4. The hydrolysis conditions depend on the nature of the protecting group. For example, when R is alkyl the hydrolysis is carried out under aqueous basic hydrolysis reaction conditions to give the corresponding acid of formula 4. The reaction is typically carried out with cesium carbonate, lithium hydroxide, and the like in an aqueous alcohol such as methanol, ethanol, and the like.

Compound 4 is then reacted with an α-aminoacetonitrile of formula 5 to give a compound of Formula (I) or (Ia). The reaction is typically carried out in the presence of a suitable coupling agent e.g., benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium

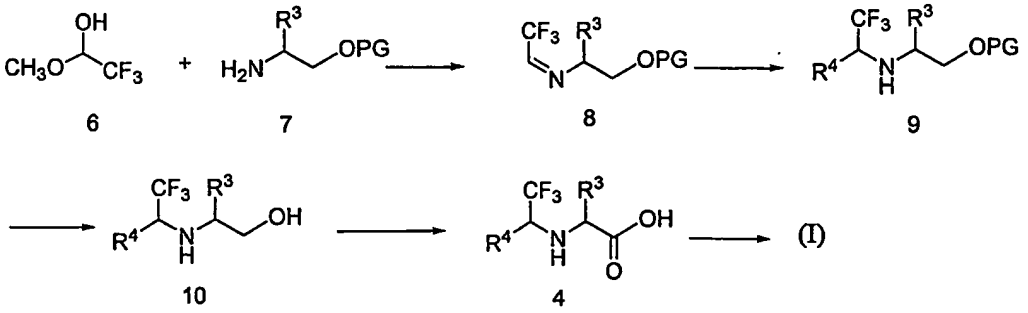
hexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), or 1,3-dicyclohexyl-carbodiimide (DCC), optionally in the presence of 1-hydroxy-benzotriazole (HOBT), and a base such as *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like. The reaction is typically carried out at 20 to 30 °C, preferably at about 25 °C, and requires 2 to 24 h to complete. Suitable reaction solvents are inert organic solvents such as halogenated organic solvents (e.g., methylene chloride, chloroform, and the like), acetonitrile, *N,N*-dimethylformamide, ethereal solvents such as tetrahydrofuran, dioxane, and the like.

Alternatively, the above coupling step can be carried out by first converting 4 into an active acid derivative such as succinimide ester and then reacting it with an amine of formula 5. The reaction typically requires 2 to 3 h to complete. The conditions utilized in this reaction depend on the nature of the active acid derivative. For example, if it is an acid chloride derivative of 4, the reaction is carried out in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, pyridine, and the like). Suitable reaction solvents are polar organic solvents such as acetonitrile, *N,N*-dimethylformamide, dichloromethane, or any suitable mixtures thereof.

It will be apparent to a person skilled in the art, that compounds of Formula (I) or (Ia) can also be prepared by first condensing 5 with the *N*-protected amino acid of formula 2 where R is hydrogen followed by removal of the amino protecting group and reacting the free amino compound with a compound of formula 1 as described in Scheme 1 above. Suitable amino acid protecting groups and reaction conditions for putting them on and removing them can be found in Greene, T.W.; and Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*; John Wiley & Sons, Inc. 1999.

Alternatively, a compound of Formula (I) or (Ia) where $R^1$, $R^2$, $R^3$, and $R^4$ are as defined in the Summary of the Invention, $R^{4a}$ is trifluoromethyl and $R^{4b}$ is hydrogen can be prepared as illustrated and described in Scheme 2 below.

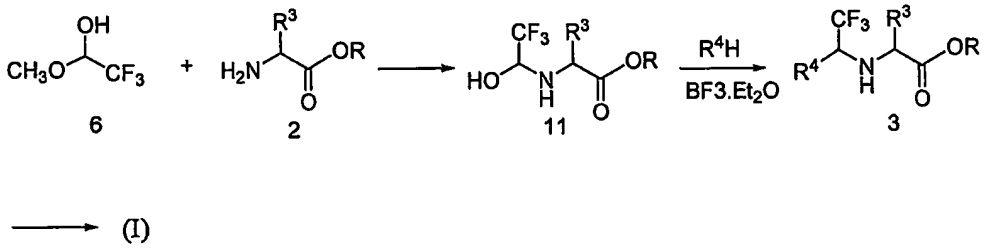
Scheme 2



Reaction of a compound of formula 7 where $R^3$ is as defined in the Summary of the Invention and PG is a suitable oxygen protecting group with a hemiacetal of formula 6 provides an imine compound of of formula 8. Treatment of 8 with an organolithium compound of formula $R^4Li$ where $R^4$ is as defined in the Summary of the Invention provides compound 9. Removal of the oxygen protecting group, followed by oxidation of the resulting alcohol 10 provides a compound of formula 4 which is then converted to a compound of Formula (I) or (Ia) as described in Scheme 1 above. Suitable oxygen protecting groups and reaction conditions for putting them on and removing them can be found in Greene, T.W.; and Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*; John Wiley & Sons, Inc. 1999.

Alternatively, a compound of Formula (I) or (Ia) where $R^1$, $R^2$, $R^3$, and $R^4$ are as defined in the Summary of the Invention, $R^{4a}$ is trifluoromethyl and $R^{4b}$ is hydrogen can be prepared as illustrated and described in Scheme 3 below.

Scheme 3

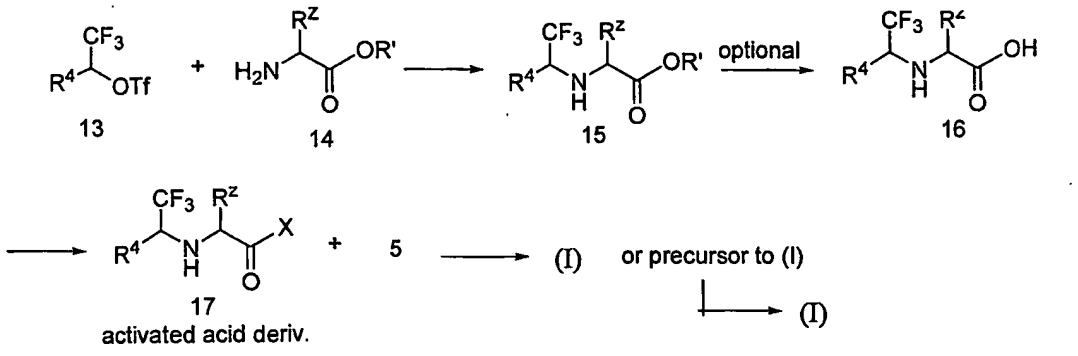



Reaction of an amino acid compound of formula 2 where R is alkyl and $R^3$ is as defined in the Summary of the Invention with a hemiacetal compound of formula 6 provides a 2-(1-hydroxy-2,2,2-trifluoroethylamino)acetate compound of formula 11. The reaction is carried out in the presence of a catalytic amount of an acid such as *p*-toluenesulfonic acid and in an aromatic hydrocarbon solvent such as toluene, benzene, and the like.

Treatment of 11 with a compound of formula $R^4H$ where $R^4$ is as defined in the Summary of the Invention under Friedel-Crafts reaction conditions provides a compound of formula 3 which is then converted to a compound of Formula (I) or (Ia) as described above.

Alternatively, a compound of Formula (I) or (Ia) where $R^1$, $R^2$, $R^3$, and $R^4$ are as defined in the Summary of the Invention, $R^{4a}$ is trifluoromethyl and $R^{4b}$ is hydrogen can be prepared as illustrated and described in Scheme 4 below.

Scheme 4




Reaction of a compound of formula 13 where $R^4$ is as defined in Summary of the Invention with a compound of formula 14 where R' is hydrogen or a carboxy protecting group and $R^z$ is $R^3$ or a precursor group (e.g., -alkylene-S-trityl or –alkylene-S-alkylene-heteroaryl) to $R^3$ group provides a compound of formula 15. The reaction is carried out in a suitable organic solvent, including but not limited to, diethyl ether, tetrahydrofuran, acetonitrile, benzene, toluene, xylene, and the like, or mixtures thereof and optionally in the presence of an organic or inorganic base. Preferably, the organic base is triethylamine, pyridine, *N*-methylmorpholine, collidine, diisopropylethylamine, and the like. Preferably, the inorganic base is cesium carbonate, sodium carbonate, sodium bicarbonate, and the like. The reaction is optionally carried out in the presence of a drying agent such as molecular sieves. Preferably, the reaction is carried out at room temperature.

Compounds of formula 13 can be prepared by methods well known in the art. For example, a compound of formula 13 where $R^4$ is phenyl or 4-fluorophenyl can be readily prepared from commercially available 2,2,2-trifluoroacetophenone or 2,2,2,4'-tetrafluoroacetophenone respectively, by reducing the keto group to an alcoholic group by suitable reducing agent such as sodium borohydride, lithium aluminum hydride, and the like. The solvent used depends on the type of reducing agent. For example, when sodium borohydride is used the reaction is carried out in an alcoholic organic solvent such as methanol, ethanol, and the like. When lithium aluminum hydride is used the reaction is carried out in an ethereal solvent such as tetrahydrofuran, and the like. Reaction of 2,2,2-trifluoro-1-phenylethanol or 2,2,2-trifluoro-1-(4-fluorophenyl)ethanol with triflic anhydride or trifluoromethanesulfonyl chloride provides the desired compound. Optically enriched compound of formula 15 can be obtained by reduction of the corresponding halogenated acetophenone with a suitable reducing agent such as catecholborane or $BH_3$-DMS complex in the presence of a suitable catalyst such as (*S*) or (*R*)-methyl CBS oxazaborolidine catalyst or (*S*) or (*R*)-α,α -diphenyl-2-pyrrolidinemethanol in the presence of 9-BBN to provide chiral alcohol

which is then converted to compound 13 as described above. Compounds of formula 14 can be prepared by methods well known in the art.

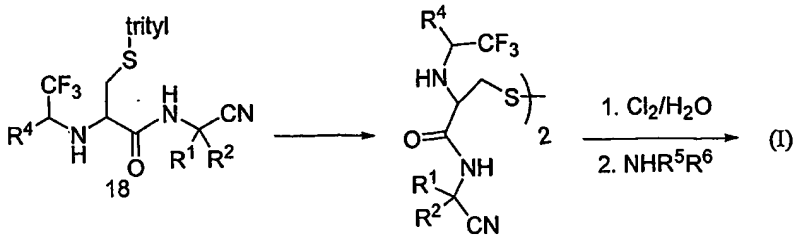
Removal of the carboxy protecting group from a compound of formula 15 where R' is a protecting group provides a compound of formula 16. The conditions used to remove the carboxy protecting group depend on the nature of the carboxy protecting group. For example, if R' is alkyl, it is removed under basic hydrolysis reaction conditions utilizing aqueous base such as aqueous lithium hydroxide, sodium hydroxide, and the like in an alcoholic solvent such as methanol, ethanol, and the like. Additionally, if the $R^z$ group in compound 14 is a precursor group to $R^3$, it can be converted to $R^3$ prior to proceeding further.

Compound 15 (where R' is hydrogen) or 16 is then converted to an activated acid derivative 17 (X is a leaving group) and which upon reaction with an aminoacetonitrile compound of formula 5 provides a compound of Formula (I) when $R^z$ is $R^3$ or a precursor compound to (I) or (Ia) when $R^z$ is a precursor group to $R^3$. The activated acid derivative can be prepared and then reacted with compound 5 in a stepwise manner or the activated acid derivative can be generated *in situ* in the presence of compound 5. For example, if the activated acid is acid halide it is first prepared by reacting 16 with a halogenating agent such as thionyl chloride, oxalyl chloride and the like and then reacted with compound 5. Alternatively, the activated acid derivative is generated *in situ* by reacting compound 16 and 5 in the presence of a suitable coupling agent e.g., benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,3-dicyclohexyl-carbodiimide (DCC), an the like, optionally in the presence of 1-hydroxybenzotriazole (HOBT), and in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine, and the like. Suitable reaction solvents are inert organic solvents such as halogenated organic solvents (e.g., methylene chloride, chloroform, and the like), acetonitrile, *N*,*N*-dimethylformamide, ethereal solvents such as tetrahydrofuran, dioxane, and the like. Alternatively, the activated acid can be reacted with $CR^1R^2(NH_2)CONH_2$ where $R^1$ and $R^2$ are as described in the Summary of the Invention, followed by conversion of the $-CONH_2$ group to the cyano group by methods well known in the art. If $R^z$ is a precursor group to $R^3$, it is converted to $R^3$ group to provide a compound of Formula (I) e.g, conversion of –alkylene-S-alkylene-heteroaryl to –alkylene-$SO_2$-alkylene-heteroaryl under oxidation reaction conditions.

Alternatively, the compound of Formula (I) or (Ia) where $R^3$ is –alkylene-$SO_2NR^5R^6$

where $R^3$ and $R^6$ are as defined in the Summary of the Invention and where $R^1$, $R^2$, $R^5$, and $R^6$ are as defined in the Summary of the Invention, $R^{4a}$ is trifluoromethyl and $R^{4b}$ is hydrogen can be prepared as illustrated and described in Scheme 5 below.

Scheme 5




Treatment of a compound of formula 18, prepared as described in Scheme 4 above, where $R^2$ is $-CH_2$-S-trityl with an oxidizing agent such as iodine in methanol to give the disulfide compound of formula 19. Oxidation of 19 with chlorine in the presence of water, followed by treatment with an amine of formula $NHR^5R^6$ in the presence of a suitable organic base such as triethylamine, diisopropylamine, pyridine, and the like, provides a compound of Formula (I) or (Ia).

Amines of formula $NHR^5R^6$ are either commercially available or they can be prepared by methods known in the art. For example, 1-cyclopropylpiperazine was prepared according to Gillaspy, M.A.; Lefker, B.A.; Hada, W.A.; Hoover, D.J *Tetrahedron Lett.* **1995**, *36*, 7399-7402. Other cyclic amines can be prepared from commercially available starting materials. For example, analogs of piperazine can be prepared from 1-*tert*-butoxycarbonylpiperazine or 1-benzyloxy-carbonylpiperazine utilizing procedures well known in the art. For example, acylation of the 4-position can be performed by treatment with an acyl chloride (*e.g.* benzoyl chloride) or sulfonylation can be achieved by treatment with a sulfonyl chloride (*e.g.* methane sulfonyl chloride) in the presence of triethylamine or diisopropylethylamine in a suitable solvent such as, but not limited to, methylene chloride. Urea formation was achieved by treatment with an isocyanate (*e.g.* isopropylisocyanate) in a suitable solvent such as methylene chloride. Alkylation was achieved using alkyl electrophiles bearing a suitable leaving group such as halide, tosylate, or triflate (*e.g.* 2,2,2-trifluoroethyl trifluoromethanesulfonate, prepared by the treatment of 2,2,2-trifuoroethanol with triflic anhydride in the presence of diisopropylethylamine in methylene chloride) in a suitable solvent such as methylene chloride or diethyl ether in the presence of triethylamine or diisopropylamine if necessary. Alkylation can also be achieved via reductive amination using a suitable aldehyde in the presence of an acid catalyst and sodium

cyanoborohydride in an acceptable solvent such as methanol. Removal of the *tert*-butyloxycarbonyl protection group can be achieved using trifluoroacetic acid in methylene chloride to produce the trifluoroacetate salt or 4 M hydrochloric acid in dioxane (Aldrich) to produce the HCl salt after solvent removal. The benzyloxycarbonyl group can be removed using 30% hydrobromic acid in acetic acid (Aldrich) in methylene chloride or by hydrogenation utilizing 10% Pd/C under an atmosphere of hydrogen gas in a suitable solvent such as ethanol. These examples are merely illustrative of some methods by which amines ($HNR^5R^6$) were made, and various modifications or additional procedures can be utilized to synthesize desirable amines and will be suggested to one skilled in the art having referred to this disclosure.

Detailed description of a compound of Formula (I) utilizing this procedure is provided in Working Example 2 below.

A compound of Formula (I) can be converted to other compounds of Formula (I). For example:

A compound of Formula (I) containing a hydroxy group may be prepared by de-alkylation/benzylation of an alkoxy/benzyloxy substituent; those containing an acid group, by hydrolysis of an ester group; and those containing a cyano, by displacement of a bromine atom on the corresponding compounds of Formula (I). A compound of Formula (I) containing a cyano group can be converted to a corresponding carboxy containing compound by hydrolysis of the cyano group. The carboxy group, in turn, can be converted to an ester group.

A compound of Formula (I) can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula (I) can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula (I) are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of Formula (I) can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula (I) can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula (I) in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of Formula (I) in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of Formula (I) can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula (I) with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula (I) can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula (I) in unoxidized form can be prepared from *N*-oxides of compounds of Formula (I) by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of Formula (I) can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula (I) with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of Formula (I) can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Compounds of the present invention may be conveniently prepared or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of Formula (I) can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diasteromeric derivatives of compounds of Formula (I), dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure

enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

Preparation of Biological Agents

In practicing this invention several processes for the generation or purification of biological agents are used. Methods for preparing the biologics are well known in the art as discussed below.

Monoclonal antibodies can be prepared using standard techniques well known in the art such as by the method of Kohler and Milstein, *Nature* **1975**, 256:495, or a modification thereof, such as described by Buck *et al.* **1982**, *In Vitro* 18:377. Typically, a mouse or rat is immunized with the MenB PS derivative conjugated to a protein carrier, boosted and the spleen (and optionally several large lymph nodes) removed and dissociated into single cells. If desired, the spleen cells may be screened (after removal of non-specifically adherent cells) by applying a cell suspension to a plate or well coated with the antigen. B-cells, expressing membrane-bound immunoglobulin specific for the antigen, will bind to the plate, and will not be rinsed away with the rest of the suspension. Resulting B-cells, or all dissociated spleen cells, are then induced to fuse with myeloma cells to form hybridomas. Representative murine myeloma lines for use in the hybridizations include those available from the American Type Culture Collection (ATCC).

Chimeric antibodies composed of human and non-human amino acid sequences may be formed from the mouse monoclonal antibody molecules to reduce their immunogenicity in humans (Winter *et al. Nature* **1991** 349:293; Lobuglio *et al. Proc. Nat. Acad. Sci.* USA **1989** 86:4220; Shaw et al. *J. Immunol.* **1987** 138:4534; and Brown *et al. Cancer Res.* **1987** 47:3577; Riechmann *et al. Nature* **1988** 332:323; Verhoeyen et al. *Science* **1988** 239:1534; and Jones et al. *Nature* **1986** 321:522; EP Publication No.519, 596, published Dec. 23, 1992; and U.K. Patent Publication No. GB 2,276,169, published Sep. 21, 1994).

Antibody molecule fragments, e.g., $F(ab')_2$, FV, and sFv molecules, that are capable of exhibiting immunological binding properties of the parent monoclonal antibody molecule can be produced using known techniques. Inbar *et al. Proc. Nat. Acad. Sci.* USA **1972** 69:2659; Hochman *et al. Biochem.* **1976** 15:2706; Ehrlich *et al. Biochem.* **1980** 19:4091; Huston *et al. Proc. Nat. Acad. Sci.* USA **1988** 85(16):5879; and U.S. Pat. Nos. 5,091,513 and 5,132,405, and U.S. Pat. No. 4,946,778.

In the alternative, a phage-display system can be used to expand the monoclonal antibody molecule populations *in vitro*. Saiki, *et al. Nature* **1986** 324:163; Scharf *et al. Science* **1986** 233:1076; U.S. Pat. Nos. 4,683,195 and 4,683,202; Yang *et al. J. Mol. Biol.* **1995** 254:392; Barbas, III *et al. Methods: Comp. Meth Enzymol.* **1995** 8:94; Barbas, III *et al. Proc. Natl. Acad. Sci.* USA **1991** 88:7978.

The coding sequences for the heavy and light chain portions of the Fab molecules selected from the phage display library can be isolated or synthesized, and cloned into any suitable vector or replicon for expression. Any suitable expression system can be used, including, for example, bacterial, yeast, insect, amphibian and mammalian systems. Expression systems in bacteria include those described in Chang *et al. Nature* **1978** 275:615, Goeddel *et al. Nature* **1979** 281:544, Goeddel *et al. Nucleic Acids Res.* **1980** 8:4057, European Application No. EP 36,776, U.S. Pat. No. 4,551,433, deBoer *et al. Proc. Natl. Acad. Sci.* USA **1983** 80:21-25, and Siebenlist *et al. Cell* **1980** 20:269.

Expression systems in yeast include those described in Hinnen *et al. Proc. Natl. Acad. Sci.* USA **1978** 75:1929, Ito *et al. J. Bacteriol.* **1983** 153:163, Kurtz *et al. Mol. Cell. Biol.* **1986** 6:142, Kunze *et al. J. Basic Microbiol.* **1985** 25:141, Gleeson *et al. J. Gen. Microbiol.* **1986** 132:3459, Roggenkamp *et al. Mol. Gen. Genet.* **1986** 202:302, Das *et al. J. Bacteriol.* **1984** 158:1165, De Louvencourt *et al. J. Bacteriol.* **1983** 154:737, Van den Berg *et al. Bio/Technology* **1990** 8:135, Kunze *et al. J. Basic Microbiol.* **1985** 25:141, Cregg *et al. Mol. Cell. Biol.* **1985** 5:3376, U.S. Pat. Nos. 4,837,148 and 4,929,555, Beach *et al. Nature* **1981** 300:706, Davidow *et al. Curr. Genet.* **1985** 10:380, Gaillardin *et al. Curr. Genet.* **1985** 10:49, Ballance *et al. Biochem. Biophys. Res. Commun.* **1983** 112:284-289, Tilburn *et al. Gene* **1983** 26:205-221, Yelton *et al. Proc. Natl. Acad. Sci.* USA **1984** 81:1470-1474, Kelly *et al. EMBO J.* **1985** 4:475479; European Application No. EP 244,234, and International Publication No. WO 91/00357.

Expression of heterologous genes in insects can be accomplished as described in U.S. Pat. No. 4,745,051, European Application Nos. EP 127,839 and EP 155,476, Vlak *et al. J. Gen. Virol.* **1988** 69:765-776, Miller *et al. Ann. Rev. Microbiol.* **1988** 42:177, Carbonell *et al. Gene* **1988** 73:409, Maeda *et al. Nature* **1985** 315:592-594, Lebacq-Verheyden *et al. Mol. Cell. Biol.* **1988** 8:3129, Smith *et al. Proc. Natl. Acad. Sci.* USA **1985** 82:8404, Miyajima *et al. Gene* **1987** 58:273, and Martin *et al. DNA* **1988** 7:99. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts are described in Luckow *et al. Bio/Technology* **1988** 6:47-55, Miller *et al. GENETIC ENGINEERING*, Setlow, J. K. *et al.* eds., Vol. 8, Plenum Publishing, pp. **1986** 277-279, and Maeda *et al. Nature* **1985** 315:592-594.

Mammalian expression can be accomplished as described in Dijkema *et al. EMBO J.* **1985** 4:761, Gorman *et al. Proc. Natl. Acad. Sci.* USA **1982** 79:6777, Boshart *et al. Cell* **1985** 41:521, and U.S. Pat. No. 4,399,216. Other features of mammalian expression can be facilitated as described in Ham *et al. Meth. Enz.* **1979** 58:44, Barnes *et al. Anal. Biochem.* **1980** 102:255, U.S. Pat. Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655 and Reissued U.S. Pat. No. RE 30,985, and in International Publication Nos. WO 90/103430, WO 87/00195.

The production of recombinant adenoviral vectors are described in U.S. Pat. No. 6,485,958.

Botulinum toxin type A can be obtained by establishing and growing cultures of *Clostridium botulinum* in a fermenter and then harvesting and purifying the fermented mixture in accordance with known procedures.

Any of the above-described protein production methods can be used to provide the biologic that would benefit from the present invention.

## Pharmacology and Utility

The compounds of the invention are selective inhibitors of cysteine proteases such as cathepsin S, K, B, and/or F, and in particular cathepsin S, and accordingly are useful for treating diseases in which cysteine protease activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention are useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, psoriasis, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders, including, but not limited to, asthma, allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts and endometriosis.

Cathepsin S is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

The cysteine protease inhibitory activities of the compounds of Formula (I) or (Ia) can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease-induced hydrolysis of a peptide-based substrate. Details of assays for measuring protease inhibitory activity are set forth in Biological Examples 1-5, *infra*.

Administration and Pharmaceutical Compositions

In general, compounds of Formula (I) or (Ia) will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula (I) or (Ia) may range from about 10 micrograms per kilogram body weight (μg/kg) per day to about 100 milligram per kilogram body weight (mg/kg) per day, typically from about 100 μg/kg/day to about 10 mg/kg/day. Therefore, a therapeutically effective amount for an 80 kg human patient may range from about 1 mg/day to about 8 g/day, typically from about 1 mg/day to about 800 mg/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula (I) or (Ia) for treating a given disease.

The compounds of Formula (I) or (Ia) can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula (I) or (Ia) in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula (I) or (Ia) in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other

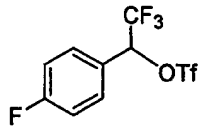
factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula (I) or (Ia) for treating a given disease will comprise from 0.01%w to 90%w, preferably 5%w to 50%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula (I) or (Ia) are described below.

Examples

The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula (I) or (Ia) (Examples) and intermediates (References) according to the invention.

Reference A

Synthesis of trifluoromethanesulfonic acid 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl ester




Step 1

To a stirred solution of 2,2,2,4'-tetrafluoroacetophenone (10 g, 52.1 mmol) in methanol (50 mL) was added $NaBH_4$ (0.98 g, 26.5 mmol) at 0° C. After stirring at 25° C for 2 h, the reaction mixture was quenched by adding 1N HCl (100 mL) and then extracted with ethyl ether. The ether extract was washed with brine, dried with $MgSO_4$, and concentrated to give 2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (11.32 g) which was used in next step without further purification.

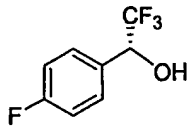
Step 2

NaH (640 mg, 16mmol, 60% in mineral oil) was washed twice with hexane (20 mL) and then suspended in dried diethyl ether (20 mL). A solution of 2,2,2-trifluoro-1-(4-fluoro-phenyl)ethanol (1.94 g, 10 mmol) in diethyl ether (10 mL) was added at 0° C. After stirring for 2 h at room temperature, a solution of trifluoromethanesulfonyl chloride (1.68 g, 10 mmol) in diethyl ether (10 mL) was added. After 2 h, the reaction mixture was quenched by adding a solution of $NaHCO_3$ and the product was extracted with diethyl ether. The extracts were washed with brine and dried, and the solvent was removed to yield trifluoromethanesulfonic

acid 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl ester (3.3 g).

Reference B

Synthesis of 2,2,2-trifluoro-1(*R*) -(4-fluorophenyl)ethanol

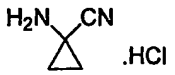


To a -78 °C toluene (25 mL)/dichloromethane (25 mL) solution of 2,2,2,4'-tetrafluoroacetophenone (2.5 g, 13.01 mmol) and 1M *S*-methyl CBS oxazaborolidine catalyst (1.3 mL, 1.3 mmol) was added freshly distilled catecholborane (1.66 mL, 15.62 mmol). The reaction mixture was maintained at -78 °C for 16 h at which time 4N HCl (5 mL in dioxane) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate and washed with a saturated brine solution. The organic layer was dried over magnesium sulfate, filtered and concentrated to provide a solid. The solid was suspended in hexanes and filtered off. The hexanes filtrate containing the desired product was concentrated and the residue subjected to flash chromatography (10 hexanes: 1 ethylacetate) to provide the title compound as colorless oil (2.2g, 87% yield). The ratio of enantiomers was determined to be 95:5 by chiral HPLC (Chiralcel OD column, 95 hexanes: 5 isopropanol mobile phase. Ret. timefor the major product was 6.757 min. Ret. time for the minor isomer was 8.274 min.).

2,2,2-Trifluoro-1(*S*)-(4-fluorophenyl)ethanol can be prepared by using *R*-methyl CBS oxazaborolidine.

Reference C

Synthesis of 1-aminocyclopropanecarbonitrile hydrochloride



Step 1

A mixture of benzophenone imine (25 g, 0.138 mol, Aldrich) and aminoacetonitrile hydrochloride (25 g, 0.270 mol, Lancaster) in dichloromethane (1000 mL) was stirred in a 2L Erlenmeyer flask under nitrogen at room temperature for 5 days. The reaction mixture was

filtered to remove the precipitated ammonium chloride and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was dissolved in ether (400 mL) washed with water (200 mL) and brine. After drying over magnesium sulfate the solution was evaporated to give (benzhydrylideneamino)-acetonitrile (47.89 g).

Step 2

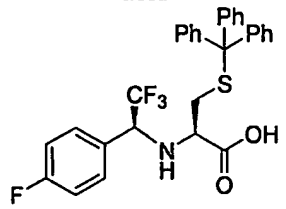
A solution of sodium hydroxide (91 g, 2.275 mol) in water (91 mL) in a 2L flask was cooled on ice under nitrogen and then treated with benzyl triethyl ammonium chloride (2.0 g, 0.0088 mol, Aldrich ) and (benzhydrylideneamino)acetonitrile (47.89 g) in toluene (100 mL). 1,2-Dibromoethane (23 mL, 122.4 mmol, Aldrich) was then added dropwise over 25 min, to the reaction mixture with mechanical stirring and cooling to maintain the internal temperature near +10 °C. The reaction mixture was then stirred vigorously for 24 h at room temperature and then poured into ice water and extracted with toluene. The combined extracts were washed with brine and then treated with $MgSO_4$ and Norite. After filtering, toluene was removed by rotary evaporation to give an oil (67 g). The residue was dissolved in boiling hexane (400 mL), treated with Norite and filtered hot and allowed to cool. A dark oil separated which was removed by pipette (~2 mL). Scratching induced crystallization in the remaining solution which was cooled on ice for 2 h. Light yellow crystals were collected by filtration and washed with cold hexane to give 1-(benzhydrylideneamino)cyclopropanecarbonitrile (30.56 g).

Step 3

A mixture of 1-(benzhydrylideneamino)cyclopropanecarbonitrile (30.56 g, 0.124 mol) in concentrated HCl (12 mL) in water (100 mL) and ether (100 mL) was stirred at room temperature for 15 h. The ether layer was discarded and the aqueous layer was washed with ether. The aqueous layer was then freeze dried to give the title compound as a tan powder (13.51 g). This compound is also commercially available.

Reference D

Synthesis of 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid

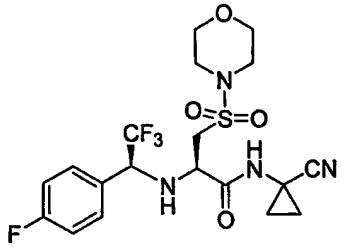



To a slurry of S-trityl-L-cysteine (4.86 g, 13.37 mmol) in dichloromethane (97 mL, 20

mL/g AA) at room temperature was added diisopropylethylamine (9.32 mL, 53.48 mmol) followed by a solution of trifluoromethanesulfonic acid 2,2,2-trifluoro-1(*RS*)-phenylethyl ester (5.32 g, 16.04 mmol) (major enantiomer (*S*), 90 ee) in dichloromethane (15 mL) via syringe all at once. After 19 h, the reaction mixture was concentrated on the rotovap to give an oil. Diethyl ether was added and the solution was washed with 1N HCl and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue with 2 hexanes/1 ethyl acetate/.25% acetic acid as the eluent provided 2(*R*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid (6 g) (major diastereomer (*R,S*), 90 de) as an oil/foam.

Example 1

Synthesis of *N*-(1-cyanocyclopropyl)-3-(morpholin-4-ylsulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide



Step 1

To a solution of morpholine (Aldrich, 1.27 mL, 14.6 mmol) and *N,N*-diisopropyl-*N*-ethylamine (DIPEA, Aldrich, 2.5 mL, 14.6 mmol) in acetonitrile (25 mL) at rt is added solid 2-benzyloxycarbonylamino-3-chlorosulfonylpropionic acid benzyl ester (3.0 g, 7.3 mmol), [prepared as described in Ross, D.L.; Skinner, C.G.; Shive, W. *J. Org. Chem.* **1959**, *24*, 1372-1374; and b) Byrnes, S.; Burckart, G. J.; Mokotoff, M. *J. Med. Chem.* **1978**, *21*, 45-49], in small portions over 10 min. A clear colorless solution resulted from which white solid began to precipitate within minutes. After 10 min, a thick white suspension was formed. The reaction was diluted in $CH_2Cl_2$ to redissolve all solids and the solution washed with 1M HCl. The aqueous layer was separated and extracted with additional $CH_2Cl_2$. The organic layer was washed with brine and dried over anhydrous $Na_2SO_4$. Following concentration *in vacuo*, 3.35 g (99%) of 2(*R*)-benzyloxycarbonylamino-3-(morpholin-4-sulfonyl)propionic acid benzyl ester was obtained as a white solid.

Step 2

To a 1/1 mixture of EtOH/EtOAc (50 mL each) was added concentrated HCl (12 M, 0.83

mL) to produce a 0.10 M solution. Solid 2(*R*)-benyloxycarbonylamino-3-(morpholin-4-sulfonyl)-propionic acid benzyl ester (0.764 g, 1.65 mmol) was dissolved in this solution with gentle heating *via* heat gun until a clear colorless solution resulted. The solution was allowed to cool to rt with $N_2$ aspiration, at which time 10% Pd/C (Aldrich, 0.300 g) was added in one portion to form a dark colored suspension. The reaction mixture was then shaken under an atmosphere of $H_2$ (50 psi) in a Parr hydrogenator for 16 h. The suspension was filtered through a pad of celite, which is then washed with several portions of MeOH. The combined organics were concentrated *in vacuo* to afford 0.593 g (quant) of 2(*R*)-amino-3-(morpholin-4-sulfonyl)-propionic acid as its HCl salt as a solid orange foam.

Step 3

To a solution of 2,2,2-trifluoromethyl-1(*R*)-(4-fluorophenyl)ethanol (0.310 g, 1.6 mmol) in $CH_2Cl_2$ at –78 °C was added DIPEA (Aldrich, 0.362 mL, 2.08 mmol) followed by trifluoromethansulfonic anhydride (Aldrich, 0.296 mL, 1.76 mmol). The solution was allowed to gradually warm to rt by allowing the cold bath to evaporate slowly. After 5 h, the reaction mixture was diluted with $Et_2O$ and quenched with 10% aqueous $NaHCO_3$. The aqueous layer was separated and extracted with $Et_2O$. The combined organics were washed with brine and dried over anhydrous $Na_2SO_4$. Following concentration *in vacuo*, 0.511 g (99%) of a brown liquid was obtained. $^1$H-NMR analysis indicated an 88/12 mixture of trifluoromethanesulfonic acid-2,2,2-trifluro-1(*R*)-(4-fluorophenyl)-ethyl ester/starting alcohol. This mixture was used without further purification.

Step 4

To a solution of trifluoromethanesulfonic acid-2,2,2-trifluro-1(*R*)-(4-fluorophenyl)ethyl ester (0.511 g, 88% pure, 1.38 mmol) in $CH_2Cl_2$ (5 mL) at rt was added DIPEA (Aldrich, 0.74 mL, 4.24 mmol) followed by the solid HCl salt of 2(*R*)-amino-3-(morpholin-4-sulfonyl)-propionic acid (0.292 g, 1.06 mmol) in small portions over 2 min. The initially homogeneous orange-brown solution became heterogeneous within minutes and was allowed to stir overnight at rt. The reaction mixture was then diluted with $Et_2O$ and quenched with 1M NaOH. The pH 14 aqueous layer was separated, washed with $Et_2O$ and acidified to pH 2 with 12M HCl. The aqueous layer was then extracted with $Et_2O$. The combined $Et_2O$ extractions of the acidic solution were washed with brine and dried over anhydrous $Na_2SO_4$. Following concentration *in vacuo*, 0.034 g (7.7%) of 3-(morpholin-4-sulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propionic acid was obtained as a colorless film.

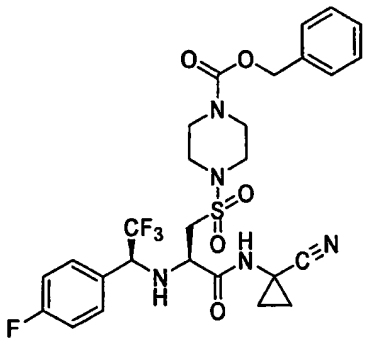
Step 5

To a solution of 3-(morpholin-4-sulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-

ethylamino]-propionic acid (0.034 g, 0.082 mmol) and the HCl salt of 1-aminocyclopropane-carbonitrile (OmegaChem, 0.013 g, 0.107 mmol) in DMF (1 mL) at rt was added solid HATU (PacificChem, 0.041 g, 0.107 mmol) in one portion followed by DIPEA (Aldrich, 0.043 mL, 0.246 mmol) to produce a bright yellow, clear solution. After stirring at rt for 1 h, the reaction was diluted in EtOAc and quenched with 10% aqueous $NaHCO_3$. Water was added to dissolve precipitated solids. The aqueous layer was separated and extracted with EtOAc. The combined organics were washed with brine and dried over anhydrous $Na_2SO_4$. Following concentration *in vacuo*, the crude product was purified by column chromatography on $SiO_2$ (2/1 EtOAc/Hex). Following concentration *in vacuo*, 0.020 g (51%) of *N*-(1-cyanocyclopropyl)-3-(morpholin-4-sulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide was obtained as a white foamy solid with repeated concentration from $CH_2Cl_2$. LC/MS: 501.4 $(M+Na)^+$; 479.3 $(M+H)^+$; 477.2 $(M-H)^-$.

Example 2

Synthesis of 4-{2-(*R*)-(1-cyanocyclopropylcarbamoyl)-2(*R*)-[2,2,2-trifluoro-1-(*S*)-(4-fluorophenyl)ethylamino]ethanesulfonyl}piperazine-1-carboxylic acid benzyl ester



Step 1

To a solution of 2(*R*)-[2,2,2-trifluoro-1-(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid (21.58 g, 40 mmol; Reference D) and 1-aminocyclopropane-carbonitrile hydrochloride (OmegaChem, 6.16 g, 52 mmol) in DMF (75 mL) at rt was added DIPEA (Aldrich, 21 mL, 120 mmol) followed by solid HATU (ChemPacific, 19.77 g, 52 mmol) in one portion. This dark, homogeneous solution was allowed to stir at rt for 24 h. The reaction mixture was quenched by addition of 10% $NaHCO_3$ (50 mL), followed by water (100 mL) and then extracted with EtOAc and the combined organics were washed with brine. Following drying over anhydrous $MgSO_4$ and concentration *in vacuo*, the resulting dark oil was chromatographed on silica gel with 3/1 hex/EtOAc elution to afford a diastereomer mixture

(ranging from 5.7/1 to 12/1) of *N*-(1-cyanocyclopropyl)-2-(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionamide and (9.83 g ) as a yellow solid.

Step 2

To a solution containing a diasteromeric mixture of *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionamide (7.0 g, 11.6 mmol) in MeOH (50 mL) at rt was added a solution of iodine (2.95 g, 11.6 mmol) in MeOH (50 mL) in one portion. The resulting dark solution was allowed to stir for 2 min and then quenched by addition of 25% aqueous $Na_2S_2O_3$ until all remaining iodine was destroyed, at which time the reaction becomes heterogeneous and white. After removing the majority of MeOH *in vacuo*, the aqueous slurry was extracted with EtOAc. The combined organic extracts were washed with brine, and dried over anhydrous $MgSO_4$. Following adsorption onto silica gel, column chromatography on silica gel with 2/1 hex/EtOAc afforded *N*-(1-cyanocyclopropyl-3-{2-(*R*)-(1-cyanocyclopropylcarbamoyl)-2-(*R*)-[2,2,2-trifluoro-1-(*S*)-(4-fluorophenyl)-ethylamino]-ethyldisulfanyl}-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide (2.6 g) of as a mixture of diastereomers.

Step 3

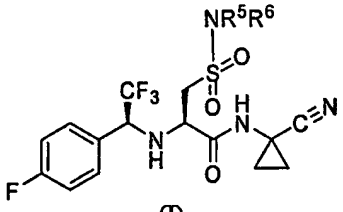
A biphasic solution of *N*-(1-cyanocyclopropyl-3-{2-(*R*)-(1-cyanocyclopropylcarbamoyl)-2 (*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]ethyldisulfanyl}-2(*R*)-[2,2,2-trifluoro-1-(*S*)-(4-fluorophenyl)ethylamino]propionamide (0.500 g, 0.694 mmol) (diastereomeric mixture) in $CH_2Cl_2$ (10 mL) and $H_2O$ (5 mL) was vigorously stirred and cooled to an internal temperature of 0 °C. Chlorine gas was slowly bubbled through the solution until the internal temperature was between 8-10 °C. Chlorine gas bubbling was ceased immediately after the internal temperature of the reaction began to recool. The reaction vessel was sealed and allowed to stir at 0 °C for 5 min. The reaction was diluted with $CH_2Cl_2$ (10 mL) and the reaction sparged with $N_2$ at 0 °C for several minutes. The organic layer is separated, and the aqueous layer extracted with $CH_2Cl_2$. The combined organics are washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a mixture of diastereomers of 2(*R*)-(1-cyanocyclopropyl-carbamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]ethanesulfonyl chloride (0.544 g) as a white to yellow-green solid that was used for subsequent reactions without further purification.

Step 4

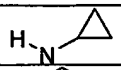
To a mixture of 1-benzyloxycarbonylpiperazine (Aldrich, 0.184 mL, 0.954 mmol) and triethylamine (Aldrich, 0.124 mL, 0.889 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was added a solution of 2(*R*)-(1-cyanocyclopropylcarbamoyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-

ethylamino]ethanesulfonyl chloride (0.272 g, 0.635 mmol) in $CH_2Cl_2$ (2 mL). The resulting yellow solution was allowed to warm to rt overnight before quenching by addition of saturated $NH_4Cl$ (3 mL). The aqueous phase was separated and extracted with $CH_2Cl_2$. The combined organics were washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting yellow residue was purified via column chromatography on silica gel using 2/1 hex/EA to 1/1 hex/EA as elutant to afford 4-{2(*R*)-(1-cyanocyclopropylcarbamoyl)-2(*R*)-[2,2,2-trifluoro-1-(*S*)-(4-fluorophenyl)ethylamino]ethanesulfonyl}piperazine-1-carboxylic acid benzyl ester (0.063 g) as a white solid that is a >13/1 ratio of diastereomers. $^1$H-NMR ($CDCl_3$, 400 MHz): δ 7.65 (s, 1H); 7.43-7.35 (m, 2H); 7.16 (m, 2H); 5.18 (s, 2H); 4.41 (q, $J$ = 6.8 Hz; 1H); 3.61 (m, 5H); 3.43 (dd, $J$ = 5.6, 14.2 Hz; 1H); 3.33 (dd, $J$ = 4.4, 13.8 Hz; 1H); 3.26 (m, 5 H); 1.59 (m, 2H); 1.25 (m, 2H). $(M+H)^+$: 612.0.

The following compounds of Formula (I) were prepared using the procedure described in Example 2 above by substituteing the appropriate amine in Step 4 above.



(I)

| R | Diastereomer ratio | $(M+H)^+$ |
|---|---|---|
|  | 5:1 | 449.0 |
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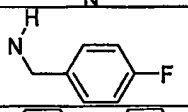
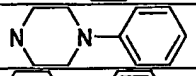
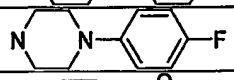
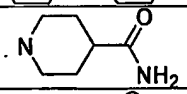
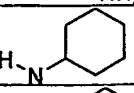
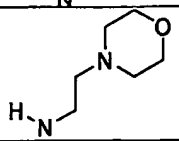
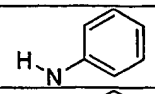
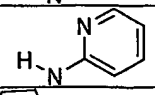
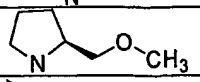
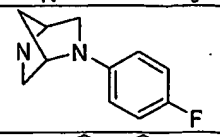
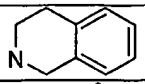
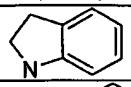
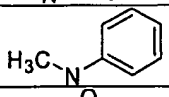
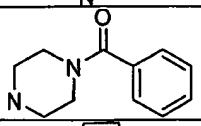
|  | 5:1 | 517.3 |
|  | 19:1 | 554.2 |
|  | >15:1 | 572.1 |
|  | 19:1 | 520.3 |
|  | 9:1 | 491.2 |
|  | 9:1 | 522.2 |

| | | |
|---|---|---|
|  | 7:1 | 485.2 |
|  | 6:1 | 486.0 |
|  | >9:1 | 507.2 |
|  | >9:1 | 584.1 |
|  | >9:1 | 525.4 |
|  | 11.5:1 | 511.2 |
|  | >13:1 | 499.4 |
|  | 49:1 | |
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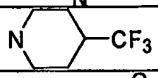
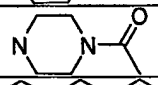
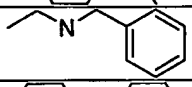
|  | >9.5:1 | 545.2 |
|  | >9.5:1 | 520.2 |
|  | >9.5:1 | 527.3 |
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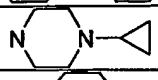
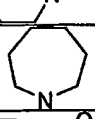
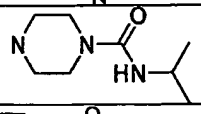
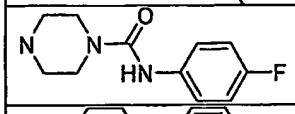
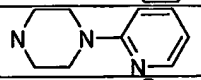
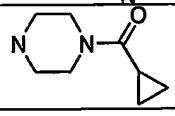
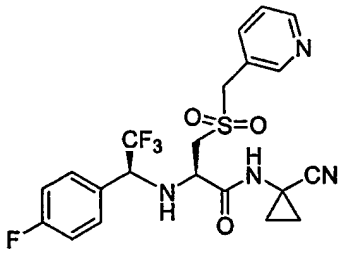
|  | 19:1 | 518.1 |
|  | >9.5:1 | 491.3 |
|  | >9.5:1 | 563.2 |
|  | >9.5:1 | 615.4 |
|  | >9.5:1 | 555.4 |
|  | >9.5:1 | 546.3 |
| | | |
| | | |

Albeit, the above compounds were obtained in diastereomeric mixture, it is well within the skill of ordinary person in the art, to separate the individual diastereomers if needed e.g., techniques such as crystallization and preparatory HPLC.

Example 3

Synthesis of *N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethylsulfonyl)propionamide



Step 1

To a solution of 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-trityl-sulfanylpropionic acid ( 539 mg, 1mmol), prepared as described in Referance D above, de 90%, in $CH_2Cl_2$ was added trifluoroacetic acid (0.4 ml, 4mmol) and triethylsilane (0.4 ml, 2mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed up to room temperature and stirred for 2 h. The solvent was removed under the reduced pressure and the residue was dissolved in 12 ml of 1N NaOH. The aqueous layer was washed with hexane and to the basic solution was added dioxane (12 ml), $P(CH_2CH_2COOH)_3$.HCl (28 mg, 0.1mmol) and 3-chloromethylpyridine (196 mg, 1.2 mmol) and the reaction mixture was stirred at room temperatute 2h. The solvent was removed under the reduced pressure and residue was acidified with 6N HCl to pH 5. The product was extracted with ethyl acetate and dried after drying the organic extracts with $MgSO_4$ the solvent was was removed to give 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethylsulfanyl)propionic acid which was used in the next step without further purification.

Step 2

2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethylsulfanyl)-propionic acid was dissolved in DMF (5 ml) and 1-aminocyclopropanecarbonitrile ( 142 mg, 1.2 mmol), HATU (456 mg, 1.2 mmol) and NMM (0.44 ml, 4 mmol) were added. After stirring for

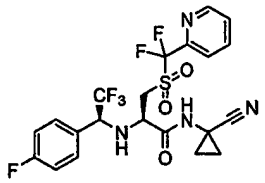
2 h at rt, saturated $NH_4Cl$ and ethyl acetate were added and stirring was continued for 20 min. The aqueous layer was extracted with ethyl acetate. The combined organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure to give *N*-(1-cyano-cyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethyl-sulfanyl)propionamide as an oil. The crude was used in the next step without further purification.

Step 3

*N*-(1-cyanocyclopropyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-(pyridin-3-ylmethylsulfanyl)propionamide was dissolved in MeOH (3 ml) and OXONE® (460 mg, 1.5 mmol) in $H_2O$ (3 ml) was added. After stirring at rt for 2 h, the solvent was removed and the residue was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The title compound was separated by Prep-HPLC.

Example 4

Synthesis of *N*-(1-cyanocyclopropyl)-3-(difluoropyridin-2-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide



Step 1

To a solution of $(Boc\text{-}Cys\text{-}OH)_2$ (20 g, 45.4 mmol) and $P(CH_2CH_2COOH)_3 \cdot HCl$ (15.61 g, 54.47 mmol) in DMF (162 mL) was added 5N KOH (109 mL) slowly over 20 min. After stirring overnight, 2-picolylchloride hydrochloride (22.34 g, 136.2 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 2.5h. The pH of the solution was adjusted to 3 with 10N HCl and the product was extracted with methylene chloride. The combined organic extract was washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give 2(*R*)-*N*-*tert*-butoxycarbonylamino-3-(pyridin-2-ylmethylsulfanyl)propionic acid which was crystallized from methylene chloride and hexane mixture to give pure product (13.70 g) as a white solid.

Step 2

2(*R*)-*N*-*tert*-Butoxycarbonylamino-3-(pyridin-2-ylmethylsulfanyl)propionic acid (3.12 g,

10 mmol) was dissolved in mixture of methanol (10 mL) and benzene (10 mL). Trimethylsilyl-diazomethane (10 mL, 2.0M solution in hexane, 20 mM) was added slowly. After 1 h, the solvent was removed to give methyl 2(*R*)-*N*-*tert*-butoxycarbonylamino-3-(pyridin-2-ylmethyl-sulfanyl)-propionate as a yellow oil.

Step 3

Methyl 2(*R*)-*N*-*tert*-butoxycarbonylamino-3-(pyridin-2-ylmethylsulfanyl)-propionate was dissolved in dioxane and 3 equiv. of 4M HCl in dioxane was added. After stirring at room temperature for 3 h, the solvent was removed under reduced pressure to give methyl 2(*R*)-amino-3-(pyridin-2-ylmethylsulfanyl)propionate hydrochloride as a hygroscopic solid.

Step 4

To a mixture of methyl 2(*R*)-amino-3-(pyridin-2-ylmethylsulfanyl)-propionate hydrochloride (1.31 g, 5 mmol), 2,2,2-trifluoro-1-(4-fluorophenyl)ethanone (0.875 g), DIPEA (2.39 g, 18.5 mmol), in dichloromethane (20 mL) was added titanium tetrachloride (4.65 mmol) dropwise over 5 min. After stirring for 3 h at ambient temperature, additional titanium tetrachloride (0.3 mmol) was added. After an additional hour of stirring, $NaCNBH_4$ (0.973 g, 15.5 mmol) was added in methanol (10 mL). After 1h, the reaction mixture was diluted with ethyl acetate (200 mL) and poured onto magnesium sulfate. After filtration and concentration, the residue was purified by flash chromatography to afford methyl 3-(pyridin-2-yl-methylsulfanyl)-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]-propionate (640 mg, 1.59 mmol).

Step 5

To a solution of methyl 3-(pyridin-2-ylmethylsulfanyl)-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]propionate (0.64 g, 1.59 mmol) in methanol (9 mL) was added 1N sodium hydroxide (4.77 mL). The resulting solution was stirred for 2 h at ambient temperature and then methanol was removed *in vacuo*. The residue was portioned between water and ethyl acetate. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were dried over magnesium sulfate. Removal of the solvents provided 3-(pyridin-2-ylmethylsulfanyl)-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]propionic acid (0.410 g, 1.06 mmol) as a white solid which was a mixture of diastereomers.

3-(Pyridin-2-ylmethylsulfanyl)-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]-propionic acid was converted to of *N*-(1-cyanocyclopropyl)-3-(pyridin-2-ylmethylsulfanyl)-2(*R*)-[2,2,2-trifluoro-1(*RS*)-(4-fluorophenyl)ethylamino]propionamide by proceeding as described in Example 2, Step 2 above. *N*-(1-Cyanocyclopropyl)-3-pyridin-2-ylmethanesulfanyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (95 mg) was obtained from

the diasteriomeric mixture by flash chromatography and was converted to *N*-(1-cyano-cyclopropyl)-3-pyridin-2-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethyl-amino)propionamide compound (50 mg) by proceeding as described in Example 3, Step 3 above.

Step 6

To *N*-(1-cyanocyclopropyl)-3-pyridin-2-ylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide (0.200 g, 0.412 mmol) in dichloromethane (5 ml) was added DIPEA (0.058 g, 4.53 mmol) and the slight suspension cooled in an ice-water bath. Boc-anhydride (0.099 mg, 0.453 mmol) was added in one portion and the resulting opaque solution was allowed to warm to ambient temperature overnight. The reaction was diluted to 100 ml with EtOAc and the organic phase extracted once with 10 ml 0.1 N HCl, sodium bicarbonate, and brine and dried over $MgSO_4$. Removal of solvent afforded [1(*R*)-(1-cyanocyclopropyl-carbamoyl)-2-(pyridin-2-ylmethanesulfonyl)ethyl]-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethyl]carbamic acid *tert*-butyl ester (0.200 g) as a white solid, which was used without further purification.

Step 7

To a 0.5M solution of potassium bis(trimethylsilyl)amide (1.02 mmol) in toluene, cooled to –78 °C, was added [1(*R*)-(1-cyanocyclopropylcarbamoyl)-2-(pyridin-2-ylmethanesulfonyl)-ethyl]-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethyl]carbamic acid *tert*-butyl ester in THF (2 ml) and the brown solution was stirred for 40 min at –78 °C. $MnBr_2$ was added as a solid, in one portion, resulting in a brown suspension. After stirring for 30 min, $(PhSO_2)_2NF$ was added as a solid and the reaction mixture was stirred at –78 °C for 30 min, then allowed to warm to ambient temperature overnight. After partitioning between 0.5 N HCl and EtOAc the organic phase was extracted with bicarbonate, brine, and dried over $MgSO_4$. The crude residue was purified via flash chromatography with EtOAc/hexanes (0 to 40% EtOAc gradient) affording the title compound. MS : 519.2, (M - H) 543.1 (M + Na) Also, *N*-(1-cyanocyclopropyl)-3-(fluoropyridin-2-ylmethanesulfonyl)-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propionamide was isolated as a diastereomeric mixture.

## Biological Examples

### Example 1

### Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: *N*,*N*-bis(2-

hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-FR-AMC (20 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 min. Apparent inhibition constants ($K_i$) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity.

Example 2

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 min. Apparent inhibition constants ($K_i$) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin K inhibitory activity.

Example 3

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 min. Apparent inhibition constants ($K_i$) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin L inhibitory activity.

Example 4

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); β-mercaptoethanol, 2.5 mM; and BSA, 0.00%. Human cathepsin S (0.05 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Val-Val-Arg-AMC (4 nMoles in 25 μL of assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (at λ 460 nm) for 5 min. Apparent inhibition constants ($K_i$) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin S inhibitory activity of < or = 100 nm.

Example 5

Cathepsin F Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); DTT, 2.5 mM; and BSA, 0.01%. Human cathepsin F (0.1 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 min at room temperature. Z-Phe-Arg-AMC (2 nMoles in 25 μL of assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (at λ 460 nm) for 5 min. Apparent inhibition constants ($K_i$) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin F inhibitory activity.

Example 1

Representative pharmaceutical formulations Containing a Compound of Formula (I)

ORAL FORMULATION

| | |
|---|---|
| Compound of Formula (I) | 10-100 mg |
| Citric Acid Monohydrate | 105 mg |
| Sodium Hydroxide | 18 mg |
| Flavoring | |
| Water | q.s. to 100 mL |

INTRAVENOUS FORMULATION

| | |
|---|---|
| Compound of Formula (I) | 0.1-10 mg |
| Dextrose Monohydrate | q.s. to make isotonic |
| Citric Acid Monohydrate | 1.05 mg |
| Sodium Hydroxide | 0.18 mg |
| Water for Injection | q.s. to 1.0 mL |

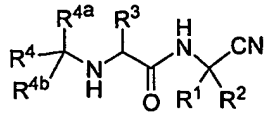
TABLET FORMULATION

| | |
|---|---|
| Compound of Formula (I) | 1% |
| Microcrystalline Cellulose | 73% |
| Stearic Acid | 25% |
| Colloidal Silica | 1% |

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

**WE CLAIM:**

1. A compound of Formula (I):



(I)

$R^1$ is hydrogen, alkyl, or haloalkyl;

$R^2$ is hydrogen, alkyl, or haloalkyl; or

$R^1$ and $R^2$ taken together with the carbon atom to which $R^1$ and $R^2$ are attached form cycloalkylene optionally substituted with one to four fluoro, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, 1,1-dioxohexahydrothiopyran-4-yl, piperidin-4-yl optionally substituted at the nitrogen atom of the piperidinyl ring with alkyl, haloalkyl, or cycloalkyl, or –$CH_2$-O-$CH_2$-;

$R^3$ is –alkylene-$SO_2NR^5R^6$ where:

$R^5$ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, –(alkylene)-$NR^7R^8$ [where $R^7$ is hydrogen, alkyl, acyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl and $R^8$ is haloalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocyloalkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonyl, aminosulfonyl, –C(O)$OR^9$ (where $R^9$ is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, or heterocycloalkyl) provided that $R^7$ is not hydrogen, alkyl, or –COR (where R is alkyl) when $R^8$ is aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl), or -$SO_2R^{10}$ (where $R^{10}$ is alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl)], acylalkyl, or heterocycloalkylaminocarbonyl; and

$R^6$ is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; or

$R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino or bridged azabicyclic ring;

wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ and the heterocycloamino and bridged azabicyclic rings formed by $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$

independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or $-SO_2R^{11}$ (where $R^{11}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano, $-CONH_2$, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino;

$R^4$ is hydrogen, alkyl, haloalkyl, aryl,heteroaryl, or heterocycloalkyl attached via a carbon ring atom, wherein the aromatic or alicyclic ring in $R^4$ is optionally substituted by one, two, or three $R^f$ independently selected from alkyl, halo, hydroxy, alkoxy, alkoxyalkyloxy, haloalkyl, haloalkoxy, carboxy, alkoxycarbonyl, cyano, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino;

$R^{4a}$ is $-CHF_2$, $-CF_3$, $-CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CCl_2CF_3$, $-CF_2CHF_2$, $-CF_2CF_2CF_3$, or $-CF_2CF_2CHF_2$; and

$R^{4b}$ is hydrogen or haloalkyl; or

a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein $R^1$ and $R^2$ are hydrogen.

3. The compound of Claim 1 wherein $R^1$ and $R^2$ together with the carbon atom to which they are attached form cycloalkylene.

4. The compound of Claim 1 wherein $R^1$ and $R^2$ together with the carbon atom to which they are attached form cyclopropylene.

5. The compound of Claim 1 wherein $R^1$ and $R^2$ together with the carbon atom to which they are attached form tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-dioxohexahydro-thiopyran-4-yl.

6. The compound of any of the Claims 2-5 wherein $R^4$ is hydrogen and $R^{4b}$ is hydrogen.

7. The compound of any of the Claims 2-5 wherein $R^4$ is hydrogen and $R^{4b}$ is haloalkyl.

8. The compound of any of the Claims 2-5 wherein $R^4$ is alkyl and $R^{4b}$ is hydrogen.

9. The compound of any of the Claims 2-5 wherein $R^4$ is alkyl and $R^{4b}$ is haloalkyl.

10. The compound of any of the Claims 2-5 wherein $R^4$ is aryl optionally substituted with one, two or three $R^f$ and $R^{4b}$ is hydrogen.

11. The compound of any of the Claims 2-5 wherein $R^4$ is aryl optionally substituted with one, two or three $R^f$ and $R^{4b}$ is haloalkyl.

12. The compound of any of the Claims 2-5 wherein $R^4$ is heteroaryl optionally substituted with one, two or three $R^f$ and $R^{4b}$ is hydrogen.

13. The compound of any of the Claims 2-5 wherein $R^4$ is heteroaryl optionally substituted with one, two or three $R^f$ and $R^{4b}$ is haloalkyl.

14. The compound of any of the Claims 2-13 wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where:

$R^5$ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, –(alkylene)-$NR^7R^8$ [where $R^7$ is hydrogen, alkyl, acyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl and $R^8$ is haloalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocyloalkylcarbonyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonyl, aminosulfonyl, –C(O)$OR^9$ (where $R^9$ is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, 4-membered heterocycloalkyl, or heterocycloalkyl) provided that $R^7$ is not hydrogen, alkyl, or –COR (where R is alkyl) when $R^8$ is aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl), or -$SO_2R^{10}$ (where $R^{10}$ is alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl)], acylalkyl, or heterocycloalkylaminocarbonyl; and

$R^6$ is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; or

$R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino or bridged azabicyclic ring;

wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ and the heterocycloamino and bridged azabicyclic rings formed by $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected

from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkylalkyl heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or $-SO_2R^{11}$ (where $R^{11}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano, $-CONH_2$, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino; provided that:

(i) when $R^5$ is hydrogen, alkyl, acyl, or haloalkyl, then $R^6$ is not hydrogen or alkyl;

(ii) when $R^5$ is hydrogen, alkyl, or acyl and $R^6$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, then the aromatic or alicylic ring in these groups has to be substituted with an $R^c$ provided that: (a) $R^c$ is not alkoxycarbonyl or an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$; and

(iii) when $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino the heterocycloamino ring has to be substituted with an $R^c$ provided that: (a) $R^c$ is not alkoxycarbonyl or an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$.

15. The compound of any of the Claims 2-13 wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where:

$R^5$ is alkoxyalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, –(alkylene)$NR^7R^8$ [where $R^7$ is hydrogen, alkyl, acyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heterocycloalkylalkyl and $R^8$ is hydroxyalkyl, alkoxyalkyl, carboxyalkyl alkoxycarbonylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonyl, aminosulfonyl, $-C(O)OR^9$ (where $R^9$ is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl,

heteroaralkyl, or heterocycloalkyl) provided that R′ is not hydrogen, alkyl, or –COR (where R is alkyl) when $R^8$ is aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl], acylalkyl, or heterocycloalkylaminocarbonyl, and

$R^6$ is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl;

wherein the aromatic or alicyclic ring in $R^5$ and $R^6$ are optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, acyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, aminosulfonyl, or $–SO_2R^{11}$ (where $R^{11}$ is alkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo.

16. The compound of any of the Claims 2-13 wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form heterocycloamino substituted one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkylalkyl, heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or $–SO_2R^{11}$ (where $R^{11}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano, $-CONH_2$, alkylaminocarbonyl,

dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino; provided that heterocycloamino ring is substituted with at least an $R^c$ provided that (a) $R^c$ is not an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$.

17. The compound of any of the Claims 2-13 wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form a bridged azabicyclic ring optionally substituted with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, acyl, acylalkyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, heterocycloalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, aminosulfonyl, or $–SO_2R^{11}$ (where $R^{11}$ is alkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, or halo; provided that heterocycloamino ring has to be substituted with an $R^c$ provided that the heterocycloamino ring is substituted with at least an $R^c$ provided that $R^c$ is not an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$.

18. The compound of any of the Claims 2-13 wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form piperazinyl or piperidin-1-yl substituted one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkylalkyl, heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered

heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or $-SO_2R^{11}$ (where $R^{11}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano, $-CONH_2$, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino; provided that heterocycloamino ring is substituted with at least an $R^c$ provided that (a) $R^c$ is not an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$.

19. The compound of any of the Claims 2-13 wherein $R^3$ is –alkylene-$SO_2NR^5R^6$ where $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form piperazinyl or piperidin-1-yl substituted at least at the 4-position of the ring with one, two, or three $R^a$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy or cyano; or optionally substituted with one or two $R^b$ independently selected from hydrogen, alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, or alkoxycarbonyl and one $R^c$ selected from hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, 4-membered heterocycloalkyl, heterocycloalkyl, 4-membered heterocycloalkylalkyl, heterocycloalkylalkyl, acyl, cycloalkylcarbonyl, 4-membered heterocycloalkylcarbonyl, acylalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaralkyloxycarbonyl, 4-membered heterocyloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, 4-membered heterocycloalkylalkyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aminocarbonyl, cycloalkylaminocarbonyl, aminosulfonyl, or $-SO_2R^{11}$ (where $R^{f1}$ is alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and further wherein the aromatic or alicyclic ring in $R^c$ is optionally substituted with one, two, or three $R^d$ independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, cyano, $-CONH_2$, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonyl, alkylsulfonyl, or alkylsulfonylamino; provided that heterocycloamino ring is substituted with at least an $R^c$ provided that (a) $R^c$ is not an acyl group that does not contain a substituted aromatic or alicyclic ring and (b) when $R^c$ is aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or cycloalkylalkyl then the aromatic or alicyclic ring in these groups is substituted with at least an $R^d$.

20. The compound of any of the Claims 2-19 wherein $R^{4a}$ is $-CF_3$ or $-CHF_2$.

21. A pharmaceutical composition comprising a compound of any of the Claims 1-20 in admixture with one or more suitable excipients.

22. A method for treating a disease in an animal mediated by Cathepsin S which method comprises administering to the animal a pharmaceutical composition comprising a compound of any of the Claims 1-20 in admixture with one or more suitable excipients.

23. The method of Claim 22 wherein the disease is rheumatoid arthritis, multiple sclerosis, myasthenia gravis, psoriasis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, asthma, pain, and atherosclerosis.

24. A method of treating a patient undergoing a therapy wherein the therapy causes an immune response in the patient comprising administering to the patient a compound of any of Claims 1-20.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/044093

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C311/07 C07C311/03 C07C311/08 C07D295/22 C07D211/96
C07D295/12 C07D213/76 C07D487/08 C07D217/08 C07D209/08
C07D207/48 C07D401/04 C07D213/32 A61K31/496 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 2005/028429 A (AXYS PHARMACEUTICALS, INC; LINK, JOHN O; MOSSMAN, CRAIG J; WOO, SOON H) 31 March 2005 (2005-03-31) claims 1,33 | 1-24 |
| A | WO 00/55125 A (AXYS PHARMACEUTICALS, INC; BRYANT, CLIFFORD, M; BUNIN, BARRY, A; KRAYN) 21 September 2000 (2000-09-21) claims 1,9,12 | 1-24 |
| A | WO 03/075836 A (MERCK FROSST CANADA & CO; AXYS PHARMACEUTICALS, INC; BAYLY, CHRISTOPHE) 18 September 2003 (2003-09-18) claims 1,17,19 | 1-24 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 3 April 2006 | 19/04/2006 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Johnson, C |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/044093

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 22-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/044093

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2005028429 A | 31-03-2005 | AU 2004274471 A1 | 31-03-2005 |
| | | CA 2521811 A1 | 31-03-2005 |
| WO 0055125 A | 21-09-2000 | AT 259782 T | 15-03-2004 |
| | | AT 299493 T | 15-07-2005 |
| | | AU 774827 B2 | 08-07-2004 |
| | | AU 3746100 A | 04-10-2000 |
| | | AU 769736 B2 | 05-02-2004 |
| | | AU 3748600 A | 04-10-2000 |
| | | BG 106003 A | 28-06-2002 |
| | | BG 106013 A | 31-05-2002 |
| | | BR 0009042 A | 26-12-2001 |
| | | BR 0009043 A | 08-01-2002 |
| | | CA 2368122 A1 | 21-09-2000 |
| | | CA 2368148 A1 | 21-09-2000 |
| | | CN 1362947 A | 07-08-2002 |
| | | CN 1364155 A | 14-08-2002 |
| | | CZ 20013217 A3 | 17-04-2002 |
| | | CZ 20013248 A3 | 17-04-2002 |
| | | DE 60008369 D1 | 25-03-2004 |
| | | DE 60021254 D1 | 18-08-2005 |
| | | DK 1178958 T3 | 21-06-2004 |
| | | EA 5369 B1 | 24-02-2005 |
| | | EE 200100485 A | 17-02-2003 |
| | | EE 200100487 A | 17-02-2003 |
| | | EP 1178958 A2 | 13-02-2002 |
| | | EP 1161415 A2 | 12-12-2001 |
| | | ES 2215626 T3 | 16-10-2004 |
| | | ES 2245303 T3 | 01-01-2006 |
| | | HK 1044755 A1 | 17-12-2004 |
| | | HR 20010737 A1 | 31-10-2002 |
| | | HR 20010738 A1 | 31-12-2002 |
| | | HU 0200347 A2 | 29-06-2002 |
| | | HU 0200503 A2 | 29-06-2002 |
| | | JP 2002539191 T | 19-11-2002 |
| | | JP 2002539192 T | 19-11-2002 |
| | | NO 20014484 A | 26-10-2001 |
| | | NO 20014485 A | 05-11-2001 |
| | | NZ 514234 A | 27-02-2004 |
| | | PL 350453 A1 | 16-12-2002 |
| | | PL 350456 A1 | 16-12-2002 |
| | | PT 1178958 T | 30-07-2004 |
| | | SK 12882001 A3 | 04-04-2002 |
| | | SK 12892001 A3 | 04-06-2002 |
| | | TR 200103337 T2 | 21-03-2002 |
| | | TR 200103390 T2 | 21-05-2002 |
| | | TR 200201874 T2 | 21-10-2002 |
| | | WO 0055126 A2 | 21-09-2000 |
| | | ZA 200107494 A | 11-09-2002 |
| | | ZA 200107495 A | 11-09-2002 |
| WO 03075836 A | 18-09-2003 | AU 2003219953 A1 | 22-09-2003 |
| | | BR 0308208 A | 11-01-2005 |
| | | CA 2477657 A1 | 18-09-2003 |
| | | CN 1638757 A | 13-07-2005 |
| | | EP 1482924 A2 | 08-12-2004 |
| | | HR 20040800 A2 | 30-04-2005 |
| | | JP 2005526753 T | 08-09-2005 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/044093

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 03075836 A | | MA 27295 A1 | 02-05-2005 |
| | | MX PA04008621 A | 06-12-2004 |